

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Joint Meeting of the Anesthetic and Life Support Drugs
Advisory Committee and the Drug Safety and Risk
Management Advisory Committee Meeting Announcement

Thursday, October 21, 2010

8:30 a.m. to 4:07 p.m.

Hilton, Washington D.C./North Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

PRECISE REPORTING, LLC

PRESENT:

Jeffrey R. Kirsh, M.D., Chair
Kalyani Bhatt, Designated Federal Officer, ALSDAC

**ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY
COMMITTEE MEMBERS (Voting)**

Jeffrey R. Kirsch, M.D., Chair
Professor and Chair,
Department of Anesthesiology and Perioperative Medicine,
Associate Dean for Clinical and Veterans Affairs,
Oregon Health & Science University,
Portland, Oregon

Randall Flick, M.D., M.P.H.,
Assistant Professor of Anesthesiology Mayo Clinic,
Rochester, Minnesota

Osemwota A. Omoigui, M.D.,
Consumer Representative,
Division of Inflammation and Pain,
Los Angeles Pain Clinic,
Hawthorne, California

Daniel Zelterman, Ph.D.,
Professor and Acting Division Head,
Division of Biostatistics, Epidemiology and
Public Health,
Yale University School of Medicine,
New Haven, Connecticut

INDUSTRY REPRESENTATIVE (Non-Voting)

Mark P. Fletcher, M.D., FAAAAI,
Acting Industry Representative,
MPF BioPharma Consultants, LLC,
Clinical Drug Development Consulting,
Charlottesville, Virginia

PRESENT: (CONTINUED)

**DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE
MEMBERS (Voting)**

Elaine H. Morrato, Dr.P.H.,
Assistant Professor,
Department of Pediatrics,
University of Colorado Denver,
Denver, Colorado

Sidney M. Wolfe, M.D.,
Consumer Representative,
Director, Health Research Group,
Public Citizen,
Washington, District of Columbia

Lewis Nelson, M.D.,
Director,
Fellowship in Medical Toxicology,
New York University School of Medicine,
New York, New York

TEMPORARY VOTING MEMBERS

Warren Bickel, Ph.D., M.D.,
Director,
Arkansas Center for Addiction Research,
Department of Anesthesia,
Brigham & University of Arkansas for Medical Sciences,
Little Rock, Arkansas

Warren B. Bilker, Ph.D.,
Professor of Biostatistics,
University of Pennsylvania,
Philadelphia, Pennsylvania

Richard Denisco, M.D.,
Medical Officer,
Pain/Addiction Medicine,
National Institutes of Health,
National Institute of Drug Abuse,
Division of Epidemiology, Services, and Prevention,
Bethesda, Maryland

PRECISE REPORTING, LLC

PRESENT: (CONTINUED)

TEMPORARY VOTING MEMBERS (CONT.)

Robert Kerns, Ph.D.,
National Program Director for Pain Management,
Yale University School of Medicine,
VA Connecticut Health Care System,
West Haven, Connecticut

Susan Krivacic,
Patient Representative,
Austin, Texas

John Mendelson, M.D.,
Senior Scientist,
Addiction and Pharmacology Research Laboratory,
California Pacific Medical Center Research Institute,
St. Luke's Hospital,
San Francisco, California

Edward Michna, M.D.,
Director,
Pain Trial Center,
Women's Hospital,
Harvard Medical School,
Boston, Massachusetts

Cynthia Morris-Kukoski, Pharm.D.,
Forensic Examiner,
Department of Justice/Federal Bureau of Investigation,
Laboratory/Chemistry Unit,
Washington, District of Columbia

Sharon Walsh, Ph.D.,
Robert Straus Behavioral Research Building,
University of Kentucky,
Lexington, Kentucky

PRESENT: (CONTINUED)

FDA MEMBERS (Non-Voting)

Ellen Fields, M.D., M.P.H.,
Team Leader,
Division of Anesthesia,
Medical Officer,
Division of Anesthesia and Analgesia Products (DAAP),
CDER, FDA

Sharon Hertz, M.D.,
Deputy Director,
Division of Anesthesia and Analgesia Products (DAAP),
CDER, FDA

Larissa Lapteva, M.D.,
Medical Officer,
Division of Anesthesia and Analgesia Products (DAAP),
CDER, FDA

Bob Rappaport, M.D.,
Director,
Division of Anesthesia and Analgesia Products (DAAP),
CDER, FDA

Judy Staffa, Ph.D., R.P.H.,
Acting Director,
Division of Epidemiology (DEPI),
CDER, FDA

Mary Willy, Ph.D.
Deputy Director,
Division of Risk Management,
Office of Surveillance and Epidemiology (OSE),
CDER, FDA

A-G-E-N-D-A

	<u>Page</u>
Call to Order, Jeffrey R. Kirsch, M.D.	9
Introduction of Committee, Jeffrey R. Kirsch, M.D.	10
Conflict of Interest Statement, Kalyani Bhatt	14
Opening Remarks, Bob Rappaport, M.D.	18

FDA Presentations:**Nature of the Problem of Prescription Opioid Misuse and Abuse**

Overview of the Risk of Abuse and Regulatory Discussions to Date to Reduce Abuse of Opioid Analgesics, Larissa Lapteva, M.D.	24
Premarketing Assessment of Abuse-deterrent Formulations, James Tolliver, Ph.D.	39
Abuse of Marketed Opioid Analgesics and Their Contribution to the National Problem of Drug Abuse, Len Paulozzi, M.D., M.P.H.	52
Clarifying Questions,	68

Data Resources and Metrics Used to Assess Prescription Opioid Misuse and Abuse

Designing Observational Studies on Drug Abuse, James C. (Jim) Anthony, Ph.D.	75
Substance Abuse and Mental Health Services Administration: Resources and Methods, Albert Woodward, Ph.D., M.B.A.	94

A-G-E-N-D-A (CONTINUED)

Page**FDA Presentations: {continued}**

Available Data Resources to Assist in Measuring Abuse
Behaviors, Patterns, and Outcomes,
Catherine Dormitzer, Ph.D. 105

Clarifying Questions, 119

Study Designs to Assess Prescription Drug Abuse

Design Considerations in Epidemiological Studies
of Abuse-deterrent Opioids,
Cynthia Kornegay, Ph.D. 134

Statistical Considerations for Epidemiological Studies
of Abuse-Deterrent Formulations,
Stephine Keeton, Ph.D. 143

Lunch, 154

Clarifying Questions, 155

Industry Presentations: Purdue Pharma, LP

Introduction,
Craig Landau, M.D. 177

Overview of Rationale and Study Program
Paul Coplan, DsC 190

Overdose Rates in OxyContin Patients and Non-Patients at
Kaiser Permanente,
Nancy Perrin, Ph.D. 204

Exposures Reported to Poison Centers,
Rick Dart, M.D., Ph.D. 214

OxyContin Abuse Among Entrants to Substance Abuse
Treatment Programs
Theresa Cassidy, M.P.H. 223

A-G-E-N-D-A (CONTINUED)

Industry Presentation: (continued)

Using Surveys to Assess the Impact of a New Formulation of OxyContin, Howard Chilcoat, ScD	228
Law Enforcement Events in the Drug Diversion Program at RADARS System, Rick Dart, M.D., Ph.D.	236
Doctor-Shopping for OxyContin as Measured by Prescription Monitoring Programs, Paul Coplan, DSc	240
Internet Discussion About Reformulated OxyContin Use, Theresa Cassidy, M.P.H.	244
Changes in Abuse Patterns in a Cohort of People Abusing OxyContin in Rural Kentucky, Carl Leukefeld, DSW	250
Summary and Conclusions, Paul Coplan, DSc	255
Clarifying Questions,	258
Adjourn,	301

P R O C E E D I N G S

(8:00 AM)

Call to Order

DR. KIRSCH: Good morning, everybody. If everyone could please take their seats, we can get started. I'd like to remind everyone present to please silence your cell phones, BlackBerrys, and other devices if you have not already done so. We'll get started by going around the table and introducing ourselves.

Before we do that, I have two other short announcements.

First, as we begin our deliberation for the members of the committee, I wanted to remind you to try to be succinct in your comments and try not to be redundant. I will, at this meeting, take the Chair's prerogative to curtail discussion that I think is redundant or not directed at the question at hand.

I'd also like to take this opportunity to wish Dr. Willy a happy birthday. Happy birthday.

(Applause.)

DR. KIRSCH: We'll start the introductions with our Industry Representative, Dr. Fletcher.

Introductions

DR. FLETCHER: Good morning. I'm Dr. Mark Fletcher. I'm the acting representative for the Anesthetics Advisory Committee, and I am a non-voting member.

DR. MENDELSON: And I'm John Mendelson. I'm an internist and clinical pharmacologist from San Francisco, and this is my first meeting.

DR. NELSON: Lewis Nelson. I'm an emergency physician and a medical toxicologist from New York University School of Medicine.

DR. KRIVACIC: I'm Susan Krivacic, and I'm a patient representative from Austin, Texas.

DR. WOLFE: I'm Sid Wolfe. I'm an internist. I'm with the Public Citizen Health Research Group on the Drug Safety and Risk Management Advisory Committee.

DR. BICKEL: Warren Bickel, Center for Addiction Research, University of Arkansas for Medical Sciences.

DR. KERNS: Good morning. I'm Bob Kerns. I'm professor of Psychiatry, Neurology, and Psychology at Yale University, and I'm also with the VA as director of

1 the Pain Management Program for VA and director of a
2 pain research center at VA Connecticut.

3 DR. BILKER: Warren Bilker. I'm Professor of
4 Biostatistics at the University of Pennsylvania.

5 DR. MORRATO: Good morning. Elaine Morrato,
6 and I'm an epidemiologist from the Colorado School of
7 Public Health and Health Systems Management and Policy.

8 DR. FLICK: Randall Flick, pediatric
9 anesthesia, intensive care, Mayo Clinic.

10 MS. BHATT: Good morning. I'm Kalyani Bhatt.
11 I'm with the Division of the Advisory Committee,
12 Consultants Management.

13 DR. KIRSCH: I'm Jeff Kirsch. I'm the chair
14 of the Department of Anesthesiology and Peri-Operative
15 Medicine at Oregon Health Sciences University, and the
16 associate dean for Clinical and Veterans' Affairs.

17 DR. ZELTERMAN: I'm Dan Zeltermann, professor
18 of Biostatistics at Yale University.

19 DR. MICHNA: Ed Michna, anesthesia, pain
20 management, Brigham and Women's Hospital in Boston.

21 DR. WALSH: Good morning. I'm Sharon Walsh.
22 I'm the director of the Center on Drug and Alcohol

1 Research and a professor in behavioral science and
2 psychiatry at the University of Kentucky in Lexington.

3 DR. OMOIGUI: Good morning. I'm Osemwota
4 Omoigui. I'm an anesthesiologist and pain specialist,
5 medical director, L.A. Pain Clinic, Hawthorne,
6 California, and also the consumer rep.

7 DR. WILLY: I'm Mary Willy. I'm deputy
8 director, Division of Risk Management in the Office of
9 Surveillance and Epidemiology.

10 DR. STAFFA: Good morning. I'm Judy Staffa.
11 I'm the acting director of the Division of Epidemiology
12 in the Office of Surveillance and epidemiology at FDA.

13 DR. FIELDS: I'm Ellen Fields, clinical team
14 leader, Division Anesthesia and Analgesia.

15 DR. LAPTEVA: Good morning, I'm Larissa
16 Lapteva. I'm deputy director for Safety in the Division
17 of Anesthesia and Analgesia Products.

18 DR. HERTZ: I'm Sharon Hertz, deputy director,
19 Division of Anesthesia and Analgesia.

20 DR. RAPPAPORT: Bob Rappaport, director,
21 Division of Anesthesia and Analgesia.

22 DR. KIRSCH: Thank you. For topics such as

1 those being discussed at today's meeting, there are
2 often a variety of opinions, some of which are quite
3 strongly held. Our goal is that today's meeting will be
4 a fair and open forum for discussion of these issues,
5 and that individuals can express their views without
6 interruption. Thus, as a gentle reminder, individuals
7 will be allowed to speak into the record only if
8 recognized by the Chair. We look forward to a
9 productive meeting.

10 In the spirit of the Federal Advisory
11 Committee Act and the Government and the Sunshine Act,
12 we ask that the Advisory Committee members take care
13 that their conversations about the topic at hand take
14 place in the open forum of the meeting. We are aware
15 that members of the media are anxious to speak with the
16 FDA about the proceedings. However, FDA will refrain
17 from discussing the details of this meeting with the
18 media until its conclusion.

19 For the convenience of the media
20 representatives, I would like to identify the FDA press
21 contact, Shelly Burgess. If you are present, please
22 stand.

1 PARTICIPANT: Shelly's not here.

2 DR. KIRSCH: Thank you.

3 Also, the committee is reminded to please
4 refrain from discussing the meeting topic during breaks
5 or lunch. Thank you.

6 I'll pass it to Kalyani, who will read the
7 Conflict of Interest statement.

8 **Conflict of Interest Statement**

9 MS. BHATT: The Food and Drug Administration
10 is convening today's Joint Meeting of the Anesthetic and
11 Life Support Drugs and Drug Safety and Risk Management
12 Advisory Committee under the authority of the Federal
13 Advisory Committee Act of 1972. All members and
14 temporary voting members of the committee or special
15 government employees or regular federal employees from
16 other agencies and are subject to Federal Conflict of
17 Interest Laws and regulations.

18 The following information on the status of
19 this committee's compliance with federal ethics and
20 conflict of interest laws covered by, but not limited
21 to, those found at 18 USC Section 208 and Section 712 of
22 the Federal Food, Drug, and Cosmetic Act is being

1 provided to participants in today's meeting and to the
2 public.

3 FDA has determined that members and temporary
4 voting members the committee are in compliance with
5 Federal Ethics and Conflict of Interest laws. Under 18
6 USC Section 208, Congress has authorized FDA to grant
7 waivers to special government employees and regular
8 federal employees who have potential financial conflicts
9 when it is determined that the agency's need for a
10 particular individual's services outweighs his or her
11 potential financial conflict of interest.

12 Under Section 712 of the Food, Drug, and
13 Cosmetic Act, Congress has authorized FDA to grant
14 waivers to special government employees and regular
15 federal employees with potential financial conflicts
16 when necessary to afford the committee essential
17 expertise.

18 Related to the discussion of today's meeting,
19 members and temporary voting members of the committees
20 have been screened for potential financial conflicts of
21 their own, as well as those imputed to them, including
22 those of their spouses or minor children and for

1 purposes of 18 USC Section 208, their employers. These
2 interests may include investments, consulting, expert
3 witness testimony, contracts, grants, CRADAs, teaching,
4 speaking, writing, patents and royalties, and primary
5 employment.

6 Today's agenda involves discussion of the
7 design of post-marketing studies of OxyContin,
8 controlled release tablets manufactured by Purdue Pharma
9 and Embeda, extended release capsules manufactured by
10 Alpharma Pharmaceuticals and King Pharmaceuticals,
11 approved for the management of moderate to severe pain
12 when a continuous, around the clock opiate analgesic is
13 needed for an extended period of time. The post-
14 marketing studies are intended to epidemiological or
15 observational studies that will assess a known, serious
16 risk of these products, and whether product-specific
17 properties which are intended to discourage misuse and
18 abuse actually result in a decrease in the risk of
19 misuse and abuse and their consequences.

20 This is a particular matter's meeting during
21 which specific matters related to Purdue's OxyContin
22 controlled release tablets and Alpha and Kings Embeda

1 extended-release capsules will be discussed.

2 Committee members and temporary voting
3 members, not conflict of interest waivers were issued in
4 connection with this meeting. To ensure transparency,
5 we encourage all standing committee members and
6 temporary voting members to disclose any public
7 statements that they have made concerning the product at
8 issue.

9 With respect to FDA's invited industry
10 representative, we would like to disclose that Dr.
11 Mark Fletcher is participating in this meeting as a non-
12 voting industry representative, acting on behalf of
13 regulated industry. Dr. Fletcher's role at this meeting
14 is to represent industry in general and not any
15 particular company. Dr. Fletcher is an independent
16 pharmaceutical industry consultant.

17 We'd like to remind members and temporary
18 voting members that if the discussions involve any other
19 products, firms, or issues not already on the agenda for
20 which an FDA participant has a personal or imputed
21 financial interest, the participants need to exclude
22 themselves from such involvement, and their exclusion

1 will be noted for the record. FDA encourages all
2 participants to advise the committees of any financial
3 relationships that they may have with any firms at
4 issue.

5 Thank you.

6 DR. KIRSCH: I'd like to recognize Dr.
7 Rappaport.

8 **Opening Remarks**

9 DR. RAPPAPORT: Good morning. Dr. Kirsch,
10 members of the anesthesia and life support drugs, and
11 the Drug Safety and Risk Management Advisory Committees,
12 invited guests, thank you for your participation in this
13 important meeting.

14 Many of you have attended some or perhaps all
15 of the numerous advisory committee meetings that we have
16 convened in the past few years to discuss applications
17 for opioid drug products that have been formulated to
18 provide some degree of abuse-deterrents. As you know,
19 one of the biggest hurdles we have to face as we review
20 these applications and decide on appropriate labeling
21 for their abuse deterrent properties is how to measure
22 their actual impact on abuse in the community.

1 For nearly a decade, we have been quite clear
2 that we would not allow language stating that a product
3 is abuse-deterrent into the labels without documentation
4 that the availability of the purportedly abused
5 deterrent product had actually reduced abuse at the
6 community level. To do otherwise would permit the
7 manufacturers to make unsubstantiated, promotional
8 claims that could lead to the same types of
9 misconceptions which resulted when OxyContin was first
10 marketed. Those misconceptions that OxyContin was less
11 likely to be abused and was less addictive than other
12 potent opioid drug products were based on just a few
13 simple words in the approved label and they played a key
14 role in the public health crisis of abuse, overdose, and
15 addiction that has plagued our communities every since.

16 Now that we have approved opioid drug products
17 with features that are intended to limit their abuse, it
18 has become even more critical for us to define a clear
19 direction for the manufacturers regarding the regulatory
20 requirements for establishing that a product has
21 demonstrated actual abuse-deterrents. To do this, we
22 must provide a scientifically and clinically sound

1 program of studies that will stand as the evidentiary
2 support for a regulatory determination.

3 But, as has been widely acknowledged in
4 numerous public meetings and in the pertinent medical
5 literature, the available databases used to track abuse
6 were not designed for this challenge, but rather to
7 detect signals of abuse. And no clear paradigm for
8 which databases and which study designs would provide
9 the best quality data for longitudinal tracking of abuse
10 in the community has been established, though many
11 different academic and other centers have been working
12 hard to address the challenge.

13 Today, we've brought together leading experts
14 from a number of disciplines that are key to the
15 development of a study or set of studies that we hope
16 will provide us with a foundation upon which we can
17 provide the guidance that is needed to support continued
18 development of these important drug products and that
19 will allow us to fulfill our regulatory mandate of
20 making decisions that are based on sound science and
21 that are not arbitrary and capricious.

22 You will be hearing from a number of FDA

1 scientists, as well as experts from other government
2 agencies and academia. In addition, representatives
3 from King Pharmaceuticals and Purdue Pharma will present
4 their proposals for studies to track abuse levels after
5 the introduction of their own novel products into the
6 market.

7 While we are not asking to judge those
8 proposals today, as they have provided them in early
9 draft form and without the benefit of agency feedback,
10 we are asking you to consider the elements of these
11 proposals as part of your discussions and in providing
12 your recommendations to us today.

13 The development of a standard by which the
14 agency can judge whether a new product has actually
15 impacted abuse in the community is a significant
16 challenge. As such, we recognize that these studies
17 that you recommend for us in this endeavor will require
18 testing and validation, and, over time, this methodology
19 will likely change and grow. We are just at the
20 beginning of this effort, and we may not have a true
21 gold standard for many years.

22 But we do have to begin someplace if we're

1 going to encourage and advance the development of abuse-
2 deterrent opioids. So, please remember that as Voltaire
3 wrote back in 1764, "the perfect is the enemy of the
4 good." And let's work together to come up with the best
5 path forward for today and perhaps for tomorrow.

6 Again, thank you for taking your time from
7 your busy schedules to participate in this important
8 process.

9 I do have one additional matter to bring to
10 your attention today before we begin the presentations.
11 Yesterday, Dr. Wolfe sent us an e-mail requesting that
12 we provide you with a copy of a warning letter that FDA
13 issued to King Pharmaceuticals regarding a video news
14 release for Embeda that we considered false or
15 misleading. We have provided that document and you will
16 find it with your package.

17 Warning letters are a type of enforcement
18 action that are used by FDA to correct promotional
19 activities that are not balanced in presenting the
20 benefits and risks of the drug or refer to unapproved
21 off-label uses. We did not include the warning letter
22 in the background package for this meeting, and

1 generally do not include them in the background package
2 for advisory committee meetings since enforcement
3 actions are not the type of scientific issues for which
4 we seek your advice.

5 Also, today's meeting is not specific to
6 Embeda. Rather, we are seeking your scientific and
7 clinical input on how best to measure the impact of
8 abuse-deterrent opioid drug products on actual abuse in
9 the community. Your recommendations will help us to
10 develop policies that will affect all companies
11 marketing or developing abuse-deterrent opioid products.

12 We have made the warning letter available to
13 you since it is available to the public on our Web Site.
14 However, the issues described in the warning letter are
15 not directly relevant to your discussions today, and
16 this meeting is not the proper forum to debate the
17 issues underlying the issuance of the letter and any
18 corrective actions taken by King Pharmaceuticals.

19 Thank you.

20 DR. KIRSCH: Thank you.

21 We'll now start the presentations by the
22 agency. The first presenter is Dr. Lapteva.

Nature of the Problem of Prescription

Opioid Misuse and Abuse

Overview of the Risk of Abuse and Regulatory Discussions to Date to Reduce Abuse of Opioid Analgesics

DR. LAPTEVA: Good morning, Mr. Chairman,
Advisory Committee Panel Members, all invited guests,
and meeting participants. My name is Larissa Lapteva,
and I work in the Division of Anesthesia and Analgesia
Products in the Office of New Drugs in CDER.

In my presentation today, I will give you a
brief overview of the risk of abuse and measures
employed to mitigate this risk. Then, briefly summarize
the current recommendations for development of abuse-
deterrent formulations, then describe formulations with
abuse-deterrent properties developed to date, and then
discuss some labeling considerations for labeling claims
for abuse deterrents.

Abuse of prescription drug products,
particularly opioid analgesics, has steeply increased
over the past decade, and is now recognized by many as a
national public health crisis. According to the recent
study report of Treatment Episode Datasets, also known

1 as TEDS, recently released by the Substance Abuse and
2 Mental Health Services Association, the proportion of
3 all substance abuse treatment admissions related to
4 serious medical outcomes associated with abuse increased
5 more than fourfold between the years of 1998 and 2008.

6 This slide presents data from the Treatment
7 Episode Dataset on the treatment admissions involving
8 opioid analgesics between the years of 1992 and 2008.
9 As you can see, the number of admissions for opioid
10 analgesics has increased from less than 30,000 in the
11 year 1992 to more than 185,000 treatment admissions in
12 the year of 2008. Such increase in the abuse-related
13 medical outcomes is likely multifactorial, but may in
14 part be explained by how these prescribed products could
15 be obtained by people who abuse and misuse opioid
16 analgesics.

17 A large proportion of the prescription opioid
18 analgesics that are misused and abused are reportedly
19 obtained by friends and relatives from patients with
20 prescriptions. On this slide, you see a pictorial
21 representation of how respondents to the National Survey
22 on Drug Use and Health, also known as NSDUH, reported

1 the source of pain-reliever that was taken non-
2 medically.

3 As you can see, about 18 percent of survey
4 respondents obtained it from one doctor, whereas about
5 70 percent obtained their pain reliever from a friend or
6 relative, either for free or because they bought it.
7 And, among the relatives, about 80 percent obtained
8 their pain relievers from one doctor. Very few obtained
9 the drugs from internet and a low proportion obtained
10 the pain reliever from more than one doctor. Given this
11 variety of sources from which an opioid analgesic could
12 be obtained, measuring non-medical use may be
13 particularly challenging. Therefore, development of
14 novel systems providing information on the patterns of
15 abuse, as well as development of formulations that deter
16 drug-seeking behaviors become an important part of abuse
17 prevention.

18 Because measurement of abuse is a developing
19 field, it is important to operate with the terms and
20 definitions that are similarly understood by all
21 parties.

22 On this slide, you see the definitions of

1 abuse and misuse proposed by the FDA Opioid REMS Working
2 Group at the Opioids REMS Class Advisory Committee
3 Meeting that was held in July of 2010. These
4 definitions of abuse and misuse will be employed by the
5 subsequent FDA presenters at this meeting.

6 Abuse is the non-medical use of a drug
7 repeatedly or even sporadically for the positive
8 psychoactive effects it produces. Misuse, on the other
9 hand, is the use of a drug outside labeling directions
10 or in a way other than prescribed or directed by a
11 health care practitioner.

12 Let me now briefly talk about the scope of
13 measures that could be employed to mitigate the risk of
14 abuse.

15 When a product with abuse potential is
16 approved, the first measure to reduce the risks
17 associated with the product is its appropriate labeling.
18 Labeling can serve is a useful, educational tool for
19 both physicians and patients. All approved controlled
20 release, high-strength opioids contain Boxed Warnings
21 that are used to convey the serious risks of this
22 product and direct the prescribing practices.

1 Medication guide is the currently used form of
2 patient-directed labeling to aide safe use of extended
3 and controlled release opioids for patients for whom
4 these products have been prescribed.

5 Strategies and public campaigns, in
6 collaboration with other agencies and stakeholder
7 organizations is another way to mitigate and prevent
8 abuse. For example, in January of 2003, FDA and SAMHSA
9 launched a joint prescription drug abuse prevention
10 educational effort with the goal of preventing and
11 reducing the abuse of narcotic opioid pain-relievers.

12 While abuse is multifactorial problem, it has
13 to be dealt with on different levels.

14 In May of 2010, the Office of National Drug
15 Control Policy released the national strategy with a
16 five-year goal to reduce non-medical use of prescribed
17 drugs and its consequences through a balanced policy of
18 abuse prevention, treatment, enforcement, and
19 international cooperation. The strategy also includes
20 efforts to reduce drug trafficking, as well as
21 prevention and treatment of drug abuse.

22 With the authorities given to the Food and

1 Drug Administration by the Food and Drug
2 Administration's Amendments Act after its passage in
3 2007, the FDA and the manufacturers of the opioid drug
4 products started developing risk evaluation and
5 mitigation strategies for classes of opioid analgesics
6 and fentanyl-containing products. These strategies
7 would put additional safeguards to the health care
8 system to aide appropriate drug prescribing, dispensing,
9 storage, and safe use.

10 While risk mitigation by information and
11 strategies, could achieve a certain degree of
12 diminishing abuse, the risk mitigation at the stage of
13 design of the pharmaceutical products appears a very
14 promising venue. Over the past decade, designing pain-
15 relief products with the new physiochemical features to
16 deter abuse has been an ongoing effort of drug
17 manufacturers and academia, highly encouraged by
18 regulatory agencies.

19 Specifically, FDA has been communicating to
20 the manufacturers about abuse deterrent formulations
21 through development of guidance documents, written
22 advice to manufacturers on individual drug development

1 programs, presentations at academic settings, and
2 discussions at advisory committee meetings.

3 Now, let me give you a brief overview of the
4 current FDA recommendations for the development of abuse
5 deterrent products.

6 Before a product is tested in preclinical
7 studies, or, as we call it, at the pre-investigational
8 new drug application stage, the agency encourages
9 manufacturers to include in the design of the
10 formulation features aiming to deter abuse. Such
11 features may include formulations with physiochemical
12 barriers to tampering or combination products with an
13 antagonist intended to reduce euphoria when the
14 antagonist is released during in appropriate use, or
15 formulations that include non-analgesic ingredients that
16 cause unpleasant side effects when the product is used
17 inappropriately.

18 At the pre-marketing stage, manufacturers
19 would need to demonstrate that the new features of the
20 formulation, in fact, translate into decrease in the
21 abuse potential, observed from different kinds of data:
22 *in vitro* data of the product's resistance to tampering,

1 as well as pharmacokinetic and bioavailability studies,
2 and clinical studies, evaluating the likeability and
3 euphorigenic effects of both manipulated and intact
4 abuse-deterrent product.

5 And finally, at the post-marketing stage,
6 manufacturers would need to demonstrate a meaningful
7 decrease in abuse-related outcomes, including addiction,
8 overdose, and death, as observed from the post-marketing
9 epidemiological studies.

10 Moving on from theory to practice, this slide
11 summarizes the regulatory experience with abuse-
12 deterrent formulations developed to date. Two approved
13 combination products formulated with an opioid
14 antagonist naloxone, Talwin, and Suboxone do have some
15 post-marketing data, which I will describe in the next
16 slide.

17 Of the other recently discussed or approved
18 abuse-deterrent products, OxyContin, reformulated from
19 the original OxyContin with a change in physicochemical
20 properties, and Embeda, oral capsule with the pellets of
21 morphine sulfate and sequestered opioid antagonist
22 naltrexon are both approved products, and their post-

1 marketing epidemiological programs are the subject of
2 this meeting's discussion.

3 Remoxy, controlled-released oxycodone,
4 formulated with additional properties to resist
5 manipulation, and Acurox, a combination product of the
6 immediate release oxycodone and niacin tablet, were both
7 designed to be abuse-deterrent, and have not yet met the
8 regulatory criteria for approval. Several other
9 products with abuse-deterrent features are currently in
10 development.

11 The story of Talwin is likely well-known to
12 this advisory committee, and probably does not need to
13 be repeated, yet, we come back to it as to an example
14 when some apparent decrease in the abuse of this product
15 was seen upon introduction of risk mitigation
16 strategies.

17 Talwin, also known pentazocine, was approved
18 in 1967 for the relief of moderate to severe pain. The
19 first reports of dependence appeared in 1968, and in the
20 late 1970s, increasing frequency of cases of abuse,
21 diversion, overdose, and death were reported. In an
22 effort to mitigate abuse, Talwin was scheduled under the

1 Controlled Substance Act in 1979, reformulated with
2 Naloxone, and the original Talwin removed from the
3 market.

4 With these measures, it appeared that the
5 abuse outcomes reported with Talwin declined during the
6 two years after withdrawal of the original formulation
7 from the market, as you can see from the graph on the
8 right side of the slide. However, while all of these
9 factors likely contributed to decrease in abuse in
10 Talwin, it was also possible that the change in the
11 availability of heroin, which occurred at about the same
12 time, played a role in decrease of abuse with Talwin.

13 This exemplifies a setting when the change in
14 abuse trends could have been influenced by multiple
15 factors and not necessarily only by the measures
16 introduced to mitigate abuse.

17 Suboxone is another formulation product
18 formulated with buprenorphine and naloxone, which was
19 approved in October of 2002 for the treatment of opioid
20 dependence. Although there have been no formal studies
21 done to assess whether addition of naloxone decreased
22 abuse, the post-marketing reports of intravenous and

1 intranasal abuse continued to support existence of abuse
2 with Suboxone, despite the inclusion of the opioid
3 antagonist in the formulation.

4 Again, on this slide and on the following
5 slide, I will briefly discuss the regulatory history of
6 OxyContin and Embeda, and then we'll move on to the
7 topic of labeling claims. But, again, the story of
8 OxyContin is well-known and does not need to be repeated
9 to this committee. However, several aspects of it
10 pertaining to the development of the reformulated
11 OxyContin are worth to mention.

12 When the growing problem with abuse and misuse
13 of OxyContin was recognized around 2001, it was as early
14 as April of 2001, when the FDA and Purdue Pharma started
15 discussing development of a reformulated product with
16 properties that would improve resistance to product's
17 manipulation. It took the company almost six years to
18 put the reformulated version through the development
19 program, and in November of 2007, the new drug
20 application for the reformulated OxyContin was
21 submitted.

22 Following the agency's review and the two

1 advisory committee meetings, the reformulated OxyContin
2 was approved in April of 2010 with two post-marketing
3 requirements: Risk Evaluation Mitigation Strategy and
4 the post-marketing epidemiological studies. While the
5 REMS is not the point of discussion of this advisory
6 committee, the epidemiologic studies will be presented
7 to the panel and discussed at this meeting.

8 Embeda is a formulation similar to another
9 extended-release morphine sulfate product named Kadian,
10 which was approved in 1996. Unlike Kadian, Embeda
11 includes the opioid antagonist naltrexone to decrease
12 the euphorigenic effects with inappropriate use. The
13 sponsor of Embeda approached the agency in
14 March 2005, before they submitted their investigational
15 new drug application, and, at the time, already planned
16 their post-marketing epidemiological program.

17 The original New Drug Application for Embeda
18 was submitted in February of 2008, and then the product
19 was approved in August of 2009 with the post-marketing
20 requirement of REMS. Discussions about the
21 epidemiological program continued in post-marketing, and
22 are the subject of this advisory committee meeting.

1 Switching gears now to the important
2 regulatory aspect of labeling claims. Before discussing
3 the labeling claims for abuse deterrence, let me explain
4 the difference between the indications and the claims.
5 Indications are the approved uses and populations for a
6 drug or biological product, and they are described in
7 the indication part of the labeling. For example, a
8 product could be indicated for treatment of moderate to
9 severe pain in opioid-tolerant patients. Claims, on the
10 other hand, may be based on any labeled information, not
11 just an indication. They may be explicit or implicit.

12 For example, if one takes a possible claim of
13 abused deterrence, then a statement in the label that
14 the product is abuse-deterrent will be an explicit
15 claim, whereas showing a table, demonstrating more
16 qualities to resist tampering with the product, would be
17 considered an implicit claim for abuse deterrence.
18 Nevertheless, implicit or explicit, claims could be
19 included in the labels when they're accurate and
20 complete reflections of the product's properties.

21 So, labeling claims for an abuse-deterrent
22 product would require demonstration that a product's

1 abuse-deterrent properties studied in the pre-marketing
2 program actually resulted in a reduction in abuse and
3 its outcomes: death, overdose, and addiction, as
4 confirmed in post-marketing epidemiological studies.
5 They would be dependent, as any claims would be
6 dependent, on the adequacy of the data. Any possible
7 promotion based on such claims would be limited to
8 presentations of the pertinent data.

9 And, in conclusion, let me highlight some of
10 the challenges with evaluating the impact of abuse-
11 deterrent formulations.

12 First of all, pre-marketing studies for abuse
13 liability have their limitations, and you will hear a
14 more extensive presentation on this topic from the
15 Controlled Substance Staff later on this morning. It is
16 difficult to measure abuse since abuse is not a clinical
17 phenomenon or a drug-related adverse reaction, but
18 rather a consequence of non-medical use. Standard data
19 collection or measures used in population-based
20 epidemiological studies may not apply to measuring
21 abuse. Current surveillance systems have their
22 limitations, of which you will hear in the subsequent

1 presentations today, and we are in need of novel
2 surveillance systems.

3 Defining the population of abusers can be
4 difficult, because usually, abusers cannot be adequately
5 identified until a serious outcome occurs or a person
6 self-identifies as a survey responder.

7 And finally, even when decrease in abuse to
8 one product is demonstrated, the overall impact on the
9 abuse problem may not be observed until more abuse-
10 deterrent formulations are on the market.

11 It is not easy to measure abuse, and it is not
12 easy to develop abuse-deterrent formulations. No single
13 government agency, individual drug manufacturer,
14 isolated non-profit or professional organization could
15 defeat this big societal problem. Collaborative, step-
16 by-step approach by multiple stakeholders will be needed
17 to achieve the desired results. Owing to the advances
18 in modern technology, designing and development of
19 abuse-deterrent formulations became possible.

20 It is now the turn of clinical and
21 biostatistical sciences to assess whether bringing these
22 formulations to the market will actually result in the

1 decrease in abuse in the nation. Through conducting
2 this advisory committee meeting, FDA is looking to an
3 open and engaging discussion to help us find the path
4 forward.

5 Thank you for your attention.

6 DR. KIRSCH: Thank you.

7 Dr. Tolliver?

8 **PreMarketing Assessment of Abuse-deterrent Formulations**

9 DR. TOLLIVER: Good morning. My name is
10 James Tolliver. I am a pharmacologist for the
11 Controlled Substance Staff within the Center of the Drug
12 Evaluation and Research at the Food and Drug
13 Administration. My presentation this morning will focus
14 on the pre-marketing assessment of abuse-deterrent
15 formulations from an FDA perspective.

16 By way of introduction, I'd like to provide
17 two definitions relevant to this presentation. The
18 first definition is that for abuse-deterrents.
19 According to the FDA-CDER draft document entitled
20 "Guidance for Industry Assessment of Abuse Potential
21 Drugs," abuse deterrence is defined as the introduction
22 of some limits or impediments to abuse in a drug

1 formulation as opposed to the outright elimination of
2 abuse.

3 The second definition is that of abuse, which
4 is defined as the non-medical use of a drug repeatedly
5 or sporadically for the positive psychoactive effects it
6 produces.

7 The pre-market assessment of formulations
8 purported to be abuse-deterrent involves a three tier
9 approach. The first tier is that of in vitro
10 manipulation and extraction studies. This is followed
11 by clinical pharmacokinetic studies on the intact and
12 manipulated formulation.

13 The last tier involves human abuse liability
14 studies. It must be stressed that the three-tier, pre-
15 market assessment is to be conducted on the to-be-
16 marketed product formulation. Such product formulations
17 usually have controlled release mechanism that allow for
18 the release of an opioid over an extended period of
19 time. These product formulations also generally contain
20 amounts of opioid that exceed that of immediate release
21 product formulations, making them potentially attractive
22 targets for manipulation with the intent to abuse.

1 There are a number of different types of
2 purported abuse-deterrent formulations for opioid
3 analgesics. Three types are presented in this slide.

4 There are formulations that are intended to
5 resist physical and chemical manipulation. A good
6 example of that is reformulated OxyContin.

7 A second type of formulation is that of an
8 opioid agonist in combination with an opioid antagonist.
9 A good example of this formulation is Embeda. With this
10 formulation, the intent is that the opioid antagonist
11 will mitigate positive, subjective effects, and possibly
12 cause adverse effects such as that of opioid withdrawal
13 if the formulated product is used in a manner other than
14 that intended in the label.

15 A third type of formulation is the combination
16 of an opioid agonist with a second component that will
17 produce an aversive effect if the product is not taken
18 as indicated. Here, an example would be Acurox.

19 The purpose of *in vitro* manipulation and
20 extraction studies is to evaluate the ease with which
21 the abuse-deterrent mechanism of a formulation can be
22 defeated. Physical and chemical manipulation of a

1 formulation is intended to obtain the opioid in a form
2 more amiable for abuse by desired routes of
3 administration.

4 In the case of opioid agonist, antagonist
5 combination formulations, separation and isolation of
6 the opioid from the opioid antagonist is a
7 consideration. For formulations of an opioid agonist
8 with an aversive agent, a goal would be to neutralize
9 the effects of the aversive agent by separation or other
10 means, while maintaining opioid agonist effects.

11 These studies are designed while keeping in
12 mind the knowledge of the physical and chemical
13 properties of the formulation, including the opioid
14 agonist, opioid antagonist, and other components, such
15 as the aversive reagent, if present.

16 Another consideration in designing these
17 studies is the knowledge of methods available to abusers
18 with different levels of chemical expertise,
19 constituting such groups as recreational abusers, more
20 experienced abusers, and, finally, so-called kitchen
21 chemists.

22 *In vitro* manipulation and extraction studies

1 are of three types. The first are studies looking at
2 the mechanical manipulation of a formulation. Secondly,
3 there are chemical extraction studies. The third type
4 of study relates to modifying the formulation in
5 whatever way for purposes of abuse by snorting,
6 inhalation, or intravenous use.

7 *In vitro* mechanical manipulation studies are
8 intended to evaluate a variety of common household tools
9 for crushing, cutting, grading, and grinding product
10 formulations with comparisons to appropriate extended-
11 release reference products. Both the time required for
12 the manipulation, as well the ease of the manipulation
13 are noted. The intent is to reduce the particle size of
14 the formulation, thereby possibly changing the
15 formulation's controlled release properties.

16 Dissolution studies of intact versus
17 manipulated product formulations will determine whether
18 the controlled release mechanism is compromised. Other
19 studies may also examine the impact of first freezing or
20 heating the formulation on the ability to mechanically
21 manipulate that formulation. Chewing simulators, using
22 artificial saliva, can be used to predict the effects of

1 chewing the product formulation on the controlled
2 release of the opioid agonist and other components of
3 the formulation.

4 *In vitro* studies also evaluate the ease of
5 chemical extraction of opioids from intact and
6 manipulated product formulations. Comparisons are also
7 to be made to intact and mechanically-manipulated
8 reference products.

9 In the case of opioid agonist/antagonist
10 combination products, consideration is given to the
11 chemical separation of the opioid agonist from the
12 opioid antagonist.

13 In chemical extraction studies, a variety of
14 chemicals are tested as solvents. These include water,
15 beverages or simulated beverages, household chemicals,
16 buffers of different ph, and other chemicals
17 constituting different molecular polarities.
18 Extractions are conducted under continuous agitation and
19 at room temperature and elevated temperature. Percent
20 of opioid extracted is determined at selected time
21 points out to 12 or 24 hours or until the opioid is
22 mostly extracted.

1 Finally, *in vitro* studies are conducted with
2 the intent of determining the ease with which a product
3 formulation may be modified mechanically and chemically
4 to prepare for abuse by intranasal inhalation and/or
5 intravenous injection. For the purpose of intranasal
6 administration, both particle size and the behavior of
7 the manipulated formulation at the lining of the nasal
8 cavity are important considerations.

9 With respect to possible inhalation, it is
10 important to consider the vaporization and degradation
11 temperatures for the opioid agonist of interest. That
12 is abuse by inhalation of an opioid is not feasible when
13 the temperature at which the opioid agonist chemically
14 decomposes is less than the temperature required to
15 vaporize the opioid agonist. In such a case, studies
16 may be done to evaluate the possible conversion of the
17 opioid agonist to a form more amiable to inhalation.

18 In the case of preparing for intravenous
19 injection, the intent is to obtain a small volume of
20 solution with sufficient opioid agonist concentration
21 such that upon intravenous injection subjective
22 reinforcing effects, such as euphoria, may be achieved.

1 The injectable solution must be of a sufficiently low
2 viscosity to allow the solution to be taken up into a
3 syringe, in other words, injectability, and subsequently
4 to be injected via needle, that is the injectability of
5 the solution.

6 Clinical pharmacokinetic studies constitute
7 the second tier of pre-market assessment, purported
8 abuse deterrent formulations. In these studies, the
9 purported abuse deterrent formulation both intact and
10 manipulated is compared to one or more reference
11 extended-release products and to a reference
12 immediately-release product.

13 Oral ingestion, in chewing or, most common
14 modes, administration with these types of studies, but
15 other routes are also found from time to time.

16 Additional studies looked at the effects of
17 Concomitant food and ethanol ingestion on the control-
18 release mechanism or purported abuse-deterrent
19 formulations.

20 These various studies tend to be open-labeled,
21 randomized, single-dosed, and crossover in design, using
22 healthy adult volunteers under opioid agonist blockade.

1 Plasma concentrations of opioid agonists and possibly
2 other metabolites of the agonist are followed as a
3 function of time following dose administration. In case
4 of an agonist-antagonist product, formulations, plasma
5 levels of the antagonist or opioid agonist are also
6 determined over time.

7 A variety of pharmacokinetic parameters are
8 determined. The most important of these includes the
9 peak plasma concentration, designated C_{max} . The time to
10 peak plasma concentration, designated T_{max} , and the area
11 under the concentration versus time curve for some time
12 from zero to some time point usually just a few hours.

13 This last parameter reflects the amount of
14 drug exposure over a designated time period. A
15 compromise of the extended-release mechanism of a
16 purported abuse-deterrent formulation is indicated when
17 the peak plasma concentration of the manipulated
18 formulation is greater than that of the peak plasma
19 concentration achieved with the intact formulation and
20 when the time to peak plasma concentration of the
21 manipulated formulation is less than that of the time to
22 peak plasma concentration of the intact preparation.

1 And finally, also, when the area over the
2 concentration curve in a short period of time for the
3 manipulation product formulation is greater than the
4 area under the concentration curve for that same period
5 of time for the intact product.

6 In that event that the results of *in vitro*
7 manipulation and extraction studies and clinical
8 pharmacokinetic studies indicate that the controlled
9 release mechanism of a purported abuse deterrent
10 formulation can be compromised. It is appropriate to
11 move to the third and final tier of the pre-market
12 assessment, namely human abuse liability studies. The
13 purpose of these studies is to compare the subjective
14 effects produced between intact and manipulated
15 formulation of the purported abuse deterrent product.
16 Additional comparisons are with subjective effects
17 produced by intact and manipulated extended release
18 reference products, as well as with an immediate release
19 reference product and possibly placebo.

20 In addition to the subject effects, another
21 pharmacokinetic dynamic effects measured,
22 pharmacokinetic parameters, as previously described, are

1 also generally determined.

2 Studies are randomized. Placebo-controlled,
3 single-dose, double-blind, crossover in design, and are
4 conducted in a controlled setting. Studies are
5 completed using approximately 30 subjects, consisting of
6 opioid-experienced, non-dependent volunteers who can
7 discriminate the subjective reinforcing effects of the
8 opioid in question from that of placebo.

9 Subjective endpoints measures are obtained
10 using a variety of standardized questionnaires used to
11 assess the reinforcing effects, such as the Visual
12 Analog Scale for drug liking, and also for dysphoric
13 effects, using, for example, the Visual Analog Scale for
14 bad drug effects. Subjective effects, as well as other
15 measurements, are recorded just before, and as a
16 function of time following treatment.

17 Maximum effect is designated as E_{max} . Time to
18 maximum effect is designated as T_{max} , and the area under
19 the time effect curve from zero to some time, t are
20 determined along with other parameters, including
21 pharmacokinetic parameters. Both mean, as well as
22 individual response data are analyzed. With respect to

1 subjective reinforcing effects, increases in the maximum
2 effect, and area under the effect curve, and a decrease
3 in the time to maximum effect of a manipulated
4 formulation compared to the intact formulation suggests
5 compromise of the controlled-release properties of the
6 formulation.

7 Human abuse liability studies do have
8 limitations. Considering that these studies involve
9 subjective measures, it is not surprising that
10 substantial variability may exist in the subjective
11 endpoints. In addition, multiple scales of subjective
12 effects may be difficult to collectively interpret.
13 Results are specific for the route of administration and
14 doses used in the study. Statistically, significant
15 differences in subjective effects may not necessarily
16 represent a meaningful difference in a potential for a
17 drug product to be abused.

18 With respect to summary and conclusion,
19 currently, pre-market marketing assessment of abuse-
20 deterrent formulations using *in vitro* manipulation and
21 extraction studies, chemical pharmacokinetic studies and
22 human abuse liability studies provide information that

1 suggests how and to what extent a product purported to
2 be abuse-deterrent may be manipulated and abused once
3 the product is on the market. However, very
4 importantly, it should be noted that only post-marketing
5 epidemiological studies will reveal the extent to which
6 a product purported to be abuse-deterrent will actually
7 be manipulated and abused after the product has been on
8 the market.

9 In addition, post-marketing epidemiological
10 studies may also establish that appropriateness of the
11 pre-market assessment studies in predicting patterns and
12 extent of abuse of products purported to be abuse-
13 deterrent once the products are placed on the market.

14 Thank you.

15 DR. KIRSCH: Thank you.

16 While Dr. Paulozzi comes up to the podium, I'd
17 like to take a minute to have Dr. Morris-Kukoski and Dr.
18 Denisco introduce themselves.

19 MS. MORRIS-KUKOSKI: Hi, Dr. Cynthia Morris-
20 Kukoski, FBI forensic examiner and toxicology at the FBI
21 Laboratory, clinical pharmacist, toxicologist, United
22 States Navy Reserve.

1 MR. DENISCO: Richard Denisco, medical officer
2 at the National Institute of Drug Abuse, specialized in
3 pain medicine and addiction medicine and public health
4 and statistics in epidemiology.

5 DR. KIRSCH: Thank you.

6 Dr. Paulozzi?

7 **Abuse of Marketed Opioid Analgesics and Their**
8 **Contribution to the National Problem of Drug Abuse**

9 MR. PAULOZZI: Good morning, everyone. My
10 name is Len Paulozzi. I'm a medical epidemiologist in
11 the National Center for Injury Prevention and Control at
12 the Centers for Disease Control and Prevention.

13 I'm going to be talking about the abuse of
14 marketed analgesics and its contribution to the national
15 problem of drug abuse.

16 When FDA asked me to cover this topic, they
17 asked me how much time I wanted. I said, well, how many
18 days do you have? And we settled on 20 minutes. So, if
19 I leave anything out, forgive me.

20 I begin many talks with this slide. It is the
21 rater of unintentional drug overdose death from all
22 drugs in the United States from 1970 through 2007, which

1 is the latest year of national mortality data being
2 available. You can see a dramatic increase in the drug
3 overdose death rate through the 1990s and through 2007.
4 The rate of 2007 actually represents about 27,700
5 deaths. The numbers of deaths related to drug overdose
6 are beginning to approach the numbers of death related
7 to motor vehicle crashes in the United States, and that
8 is an unprecedented occurrence.

9 Why is the rate going up? We have some data
10 that breaks down the drug types from 1999 through 2007
11 shown here on this slide. The occurrence of drugs are
12 dependent on the coroner or medical examiner putting
13 down the name of the drug on the death certificate.
14 Some death certificates still come in as recorded as
15 drug overdose and nothing else or a narcotic overdose or
16 even opioid overdose, and you can't tell what kind of
17 drug it is exactly. This data represents death
18 certificates where they do specify the type of drug.
19 And, of course, many or most deaths involve more than
20 one type of drug.

21 So, some deaths are represented twice on this
22 slide. But the point is that the opioid analgesic-

1 related deaths have increased more rapidly than any
2 other of the major types of drugs shown here on this
3 slide.

4 Heroin deaths are basically flat from 1999
5 through 2007. Cocaine deaths have gone up appreciably,
6 but the biggest increase is in the opioid analgesic
7 category. And it was actually a few years ago that the
8 total number of deaths involving opioid
9 analgesics exceed the total number involving either
10 heroin or cocaine in the United States.

11 The number of deaths shown here for opioid
12 analgesics and unintentional overdoses shown in yellow
13 is the same as on the previous slide. What I've added
14 to it is the opioid sales in the United States as
15 tracked by the Drug Enforcement Administration ARCOS
16 Program, and computed milligrams in morphine milligram
17 equivalents per person over time.

18 The opioid sales are shown on the right axis,
19 and they have increased dramatically up to the point in
20 2007. Preliminary figures show about 700 milligrams per
21 person being distributed of opioid analgesics in the
22 United States. And, clearly, the increases have

1 occurred in parallel.

2 Turning from mortality data for a moment, this
3 is data from emergency department visits as recorded by
4 the Drug Abuse Warning Network. It's a sample of
5 emergency departments across the United States and the
6 numbers are projected upward to national estimates. And
7 in 2008, the numbers of ED visits involving legal drugs,
8 the first bar on the left in yellow, from misuse or
9 abuse of those drugs surpassed 1 million emergency
10 department visits. Therefore, the number of visits
11 involving legal drugs exceeded the number involving
12 illicit drugs shown in the first bar in green. Opioid
13 analgesics and benzodiazepines were the major
14 contributors to the legal drug category, whereas cocaine
15 and heroin were the major contributors to the illicit
16 drugs in emergency department visits.

17 Although there are thousands of deaths
18 associated with opioid analgesics in the United States
19 today, they really are the tip of the iceberg or the top
20 of the pyramid, if you prefer. I put the unintentional
21 overdose deaths related to opioid analgesics at the top
22 here, and in 2007, there were at least 11,499 documented

1 involvement of opioid analgesics on death certificates
2 in the United States.

3 By comparison, there are about 105,000 opioid
4 treatment admissions, where opioid analgesics were the
5 primary drug. There were about 306,000 ED visits for
6 the misuse or abuse of opioid analgesics. That's about
7 27 ED visits for every one death. And data from the
8 National Survey of Drug Use and Health shows that in
9 2009, there were almost 2 million people in the United
10 States who self-reported abuse or dependence on opioid
11 analgesics in the past year. And the largest figure of
12 all is the 5.3 million people who reported non-medical
13 use of opioid analgesics in the past month on the 2009
14 national survey of Drug Use and Health.

15 So, as the deaths have gone up, they really
16 are just representing a small part of the morbidity and
17 mortality associated with this problem, which affects
18 millions of people now in the United States.

19 So, I'm now going to turn to some different
20 sources of data to try to quantify the prevalence of
21 abuse of opioid analgesics using a variety of different
22 data sources. We're going to look at some circumstances

1 of pharmaceutical overdose deaths in medical examiner
2 studies. These are state-specific studies, look at some
3 results of urine drug testing among pain patients in
4 brief, data on patients receiving opioid analgesics
5 tracked in insurance claims data or Prescription Drug
6 Monitoring Program information, and data on the route of
7 administration or exposure of people entering substance
8 abuse treatment because that's the topic of this
9 meeting.

10 First, the overdose deaths and medical
11 examiner data. This was one of the earlier studies that
12 we conducted on this topic in the State of West
13 Virginia, which, at the time, had the highest drug
14 overdose rate in the United States. The years 2006,
15 West Virginia was affected primarily by legal drugs
16 rather than illicit drugs. In that year, 295
17 pharmaceutical overdose deaths occurred in West
18 Virginia.

19 Within that group, 231 decedents, or 78
20 percent, had a history of substance abuse, whether
21 alcohol or drugs. Other mental illness other than
22 substance abuse was observed or noted in the medical

1 examiner's records for 43 percent of the decedents. And
2 63 percent of the decedents had one or more of the
3 prescription drugs involved in their death for which
4 they did not have any prescription recorded in the State
5 Prescription Drug Monitoring Program. Twenty-two
6 percent of the deaths showed some evidence of non-
7 medical route of administration, such as injection or
8 snorting the drugs. Twenty-one percent had a history of
9 five or more prescribers of controlled substances in the
10 past year in the State Prescription Drug Monitoring
11 Program, and about seventeen percent had a history of a
12 previous overdose.

13 All told, a population that had a lot of
14 indicators of history of substance abuse and their past
15 history and then the circumstances surrounding their
16 death.

17 Another study done more recently in Utah, 2008
18 and 2009, involving a 155 deaths. Similar results,
19 history of substance abuse in 60 percent, signs of non-
20 medical use, in this case a broad definition, were found
21 in 51 percent, but that category includes any opioid
22 involved without a prescription, which was involved in

1 37 percent of the decedents. Again, linking decedents
2 to the State Prescription Drug Monitoring Program.
3 Eighty-two percent had a history of chronic pain.
4 Typically, this was headaches or back pain or other
5 muscular skeletal problems, and 57 percent had mental
6 illness and that had been diagnosed by a provider and
7 was available to the state medical examiner.

8 This is the data from a Web report put out by
9 the Ohio Department of Death recently for data for 2006
10 through 2008. They were able to look at some indicators
11 of substance abuse by linking their deaths, again, with
12 their State Prescription Drug Monitoring Program. And
13 they looked at unintentional drug overdose deaths in
14 total, over 1,000 deaths in Ohio during these three
15 years. And 16 percent of those individuals had filled
16 prescriptions from an average of 5 prescribers per year
17 over the three years of data that they looked at. And
18 I'm going to show you a lot of information about numbers
19 of prescribers that's oftentimes used as a surrogate for
20 a label of doctor shopping, a use of multiple providers
21 to obtain similar types of drugs.

22 As in previous studies, a lot of the people

1 had no prescriptions in the Prescription Drug Monitoring
2 Program for the drugs in their death; in this case for
3 the opioids. Twenty-five percent had no prescription,
4 so, they obtained the drug by some route other than
5 through prescription, through drug diversion,
6 presumably. And they looked in particular at methadone
7 because it was the leading drug among the deaths
8 involved, and they saw that 71 percent, most of the
9 people, had no prescription in the Prescription Drug
10 Monitoring Program for methadone among the methadone-
11 related deaths. Methadone, of course, is also used in
12 substance abuse treatment programs and rather than just
13 for treatment of pain.

14 And this is sort of a compilation of a number
15 of studies focused on methadone. It was the leading
16 drug among opioid analgesic deaths in the United States
17 for most of this decade. It's only in the last few
18 years that state studies have shown that oxycodone has
19 come back up to the top. But, in general, as seen for
20 the other drugs, a small proportion of the decedents had
21 a prescription. That's the last column, percent with
22 prescription. Going back to early studies through the

1 1990s, it's basically a third or so of the people had a
2 prescription for methadone when examined by the medical
3 examiner.

4 So, you can see a variety of different
5 problems around the country in different states, taken a
6 look at by medical examiners, sometimes using different
7 definitions. It's hard to standardize some of the
8 information, but there's a large prevalence of abuse
9 associated with opioid analgesic deaths.

10 Turning to another topic, patients with
11 chronic nonmalignant pain, a lot of literature, again,
12 on this topic. Many studies. I chose just to present
13 to you this one systematic review of the literature.
14 It's prevalence of abuse-related behaviors in patients
15 with chronic non-cancer pain and chronic opioid
16 analgesic treatment. And Fishbain in this 2008 paper
17 reviewed a number of these studies and pulled out a
18 number of different prevalences from them. The
19 clinician-determined development of addiction was
20 recorded in a number of different ways and different
21 studies, among 24 studies that looked at this prevalence
22 of addiction among these patients under treatment.

1 Three percent were recognized as having or recorded as
2 having addiction. However, when they looked at the
3 percent of patients in 17 studies with aberrant drug-
4 related behaviors, things such as reporting a loss of
5 your prescription, early refills, calls to the office,
6 antagonistic behavior, a variety of different measures
7 in different studies, 11 percent was the prevalence.

8 And finally, in 5 studies, aberrant behaviors
9 determined by urine drug testing showed the highest
10 prevalence of all, about 20 percent. Aberrant behaviors
11 in this case meant that the person did not have the
12 prescribed opioid in their urine when tested or they had
13 opioids that were not prescribed to them in their urine.
14 Either one qualified as aberrant behaviors. And this
15 generally recognized that observation and even
16 questionnaires administered to patients are not very
17 sensitive to the overall prevalence of this problem.

18 And, more recently, people are looking at
19 large datasets, such as insurance claims and
20 Prescription Drug Monitoring Programs to try to get a
21 handle on this using surrogate markers for a misuse and
22 abuse of drugs.

1 This a study in Maine based on insurance
2 claims data published by White last year. They looked
3 at behaviors during just a three-month period of time,
4 and these are all privately-insured patients who were
5 all opioid users. If you look at the bottom, the lowest
6 row, opioid abuse, diagnosis, and claims data, 3.5
7 percent. That's actually, therefore, observed by
8 clinicians and recorded as a diagnosis. It's similar to
9 the 3.3 percent I showed on a previous slide for
10 recognized addictions by clinicians.

11 They also looked at combinations of
12 prescription claims and identified people who had used
13 two or more pharmacies for opioids; about 20 percent
14 during 3 months. Twenty-six percent used two or more
15 prescribers. Sixteen had one plus early refill or an
16 opioid prescription. Certainly not pathognomonic or all
17 indicative of misuse or abuse necessarily, but they did
18 find the significant associations between these
19 behaviors, these uses of multiple pharmacies,
20 physicians, and early refills with the presence of an
21 opioid abuse diagnosis in claims data. So, it is a
22 marker, although a non-specific one, for opioid abuse.

1 The recent study from California Prescription
2 Drug Monitoring Program using 2007 data, they looked at
3 the prevalence of the same drug obtained from two or
4 more prescribers and dispensed at two or more pharmacies
5 within 30 days, a fairly tightly-circumscribed
6 definition in 2007, they looked at different classes of
7 drugs, and they found that for opioid analgesics
8 prescriptions, 12.8 percent of all the prescriptions
9 were involved in this type of a situation, use of two or
10 more prescribers, two or more dispensers, and so on.

11 Benzodiazepine is 4.2 percent, smaller
12 percentages for stimulants and so on. Eight point four
13 percent overall for any Schedule II through IV
14 controlled prescription drug. Again, use of two doctors
15 and two pharmacies is not necessarily indicative of
16 abuse, but that may happen through people legitimately
17 losing their prescriptions or choosing to go to
18 different pharmacies. But the percentages that might
19 happen by such innocent occurrences might be represented
20 by the 1 percent stimulant or an anorectic, and,
21 therefore, the difference between that and the 12.8
22 percent of all opioid prescriptions meeting this

1 definition, I think, is remarkable.

2 Another study from Massachusetts in 2006 used
3 slightly different definitions. There's really no
4 consistent definitions of doctor shopping in studies to
5 date. They looked at use of three or more prescribers
6 of Schedule II drugs, which is primarily opioid
7 analgesics in the State Prescription Drug Monitoring
8 Program. Found that it was about 8 percent of patients
9 had used 3 or more prescribers during one year, and
10 about 2.5 percent had used 3 or more pharmacies.

11 When they combined prescribers and pharmacies,
12 you can see the numbers in the last column. They gave
13 the data only in terms of the percent of prescriptions.
14 So, 7.7 percent of Schedule II prescriptions were
15 included in this definition, 3 or more prescribers and
16 pharmacies. Correspondingly, smaller percentages with
17 larger numbers of prescribers and pharmacies.

18 Finally, some data collected by surveying
19 State Prescription Drug Monitoring Programs. This data
20 comes from the PMP Center of Excellence at Brandeis
21 University, and it is a survey of Bureau of Justice
22 Assistance Funded Harold Rogers Grantees among the State

1 Prescription Drug Monitoring Programs. They looked at
2 the numbers of either individuals or doses that met
3 their definition of doctor shopping, which was five plus
4 prescribers and five plus pharmacies in six months. The
5 prevalence among individuals was .4 percent, using data
6 from 7 PDMPs, and for doses, it was 1 percent of all
7 these Schedule II through IV prescriptions.

8 So, as you can see, the as definitions get
9 tighter, as the numbers of prescribers and pharmacies
10 goes up, the prevalence goes down. It makes sense.

11 Lastly, route of exposure, I included just two
12 slides here to give what there is available about route
13 of exposure, given the topic of this meeting. This is
14 information from Butler from a surveillance system known
15 as NAVIPPRO, data from 2007 and 2008. This is from
16 adult drug-users entering substance abuse treatment
17 using opioid analgesics, and it asked them about their
18 routes of administration, and they could record more
19 than one route of administration per type of opioid
20 analgesic.

21 So, for oxycodone, 76 percent of the users
22 reported that they used it orally some of the time, and

1 that would include chewing and sublingual exposures.
2 Forty-five percent inhaled, thirteen percent injected,
3 smaller percentages smoked and used other routes of
4 exposure. For morphine, 40 percent oral, 29 percent
5 inhaled, 56 percent injected. Again, more than one
6 route of exposure is reported here, obviously, because
7 these numbers add up to more than 100 percent.

8 There is comparable data available from the
9 treatment data exposure dataset of the Substance Abuse
10 and Mental Health Services Administration, also known as
11 TEDS. This is data from 2008 shown in the last column.
12 The difference here is that TEDS looks the at most
13 commonly used or records the most commonly used route of
14 exposure, and this is just oxycodone because that's all
15 that TEDS had information on. But I think the numbers
16 are basically consistent with the NAVIPPRO statistics,
17 which I've repeated in the first column here.
18 Basically, the most common route is oral, including
19 chewing, 30 percent inhaled, 13 percent injected, and
20 smaller percentages for smoking and other routes of
21 exposure. And my thanks to Deborah Trunzo for
22 generating this information for me. Deborah's with

1 SAMHSA Group.

2 And that's all I have. Thank you.

3 DR. KIRSCH: Thank you. We now have a few
4 minutes to ask the speakers clarifying questions. The
5 way that I like to run this part of it is if you raise
6 your hand, we'll mark you down and call on you by
7 individual.

8 Dr. Bickler? I'm sorry, Dr. Bickel?

9 **Clarifying Questions**

10 DR. BICKEL: I do like Dr. Bickler's name
11 though overall. It's very nice.

12 (Laughter.)

13 I have sort of a comment and an inquiry for
14 Dr. Tolliver, and I agree with your assessment,
15 generally speaking, right, that abuse liability
16 approaches are using methodological procedures that are
17 in excess of 30-years-old and have certain limitations
18 about them. however, there have been dramatic advances
19 in the study of behavioral economics of the consumption
20 of additive commodities that show increased sensitivity,
21 a greater selectivity, and have been demonstrated to
22 being increasingly predictive of subsequent behavior. I

1 was wondering if you have considered or the FDA has
2 considered updating their methods to the more novel
3 approaches that have been demonstrating those effects.

4 DR. TOLLIVER: I think for the most part, the
5 abuse, the human abuse liability studies that I
6 mentioned are the ones that we've been using. I don't
7 know if that answers the question or not.

8 DR. BICKEL: So, I guess I would just suggest
9 that you contemplate or look into the options of
10 updating some of these methodological procedures using
11 more recent events as an understanding how reinforcing
12 substances are influenced choice across a broad set of
13 conditions as indicated by behavioral economics.

14 DR. TOLLIVER: All right.

15 DR. KIRSCH: Dr. Morrato?

16 DR. MORRATO: Thank you. I had a clarifying
17 question with regard to definition of claims, and since
18 we'll be talking about what's the evidence needed to put
19 something into label or to make a claim.

20 I was wondering if there's any precedent or
21 examples that we could work from that talks about claims
22 that might be time-dependent. So, an easy one would be

1 this is the drug that's number one prescribed, and that
2 changes over time. So, are there examples within the
3 FDA in which a claim gets into the label, it needs to be
4 monitored over time because it's a time-dependent kind
5 of claim, and, therefore, what's the process of taking a
6 claim out once it's in and how long that takes, et
7 cetera?

8 DR. RAPPAPORT: I can't think of an example,
9 but, certainly, we modify the label all the time as new
10 information becomes available. I will say it's more
11 difficult once something gets in there to take it out.
12 But not terribly difficult. We still can do it.

13 If the information in there is found to be
14 incorrect and raises safety concerns, we can get it out
15 of there. But to modify the label as time goes on, we
16 do that when it's essential to do so. We can't make
17 changes to every label, to every sentence in every label
18 because of minor changes, but if there are significant
19 changes, we do work with the companies to make those.

20 Does that address your question?

21 DR. MORRATO: I think so. So, the norm is you
22 get data and you put a statement into the label as

1 opposed to a type of claim that you know could be
2 changing and evolving over time, such as is it abuse-
3 deterrent? That's not the normal type of claim that
4 ends up in a label. It's more like an absolute fact.
5 It has this benefit, it has this side effect, but still
6 evolving --

7 DR. RAPPAPORT: Yes, we only allow into the
8 label whatever is supported by data. So, if there's no
9 data at this time to support that something is abuse-
10 deterrent in the community, it's not going in the label.
11 If that changes in time, we'd be only too happy to get
12 it into the label because I think that would be
13 beneficial to the community and to prescribers.

14 DR. MORRATO: Right. I was just talking about
15 the case in which it got into the label, but then, over
16 time, you don't see it, and --

17 DR. RAPPAPORT: We had to change it. We could
18 take it out.

19 DR. MORRATO: Yes.

20 DR. RAPPAPORT: Yes.

21 Sharon, did you want to add something?

22 DR. KIRSCH: Dr. Nelson?

1 DR. NELSON: Thanks. Just another question
2 for Dr. Tolliver.

3 DR. KIRSCH: Okay.

4 DR. NELSON: Just my assumption is that the
5 three-tiered approach you outlined is a regulatory
6 requirement. Is that right? Or is that just something
7 that most companies do before they market a drug?

8 DR. TOLLIVER: I don't know that it's a
9 "regulatory requirement." I don't think that we have
10 specific guidance in place right now. However, the kind
11 of data that I provided to you today or the kind of
12 studies are what are provided to the Food and Drug
13 Administration for us to look at with respect to
14 evaluating the abuse --

15 DR. NELSON: Okay, can I --

16 DR. HERTZ: These are -- excuse me.

17 DR. NELSON: Sorry.

18 DR. HERTZ: These are recommendations that
19 have evolved as we started to interact with companies
20 who have been seeking different approaches to developing
21 these products. It's been informed in part by
22 discussions at advisory committees, as well. So, it's

1 not a regulatory requirement, but it is the
2 recommendation so we can begin to understand sort of in
3 a step-wise manner what different formulations'
4 characteristics are.

5 DR. NELSON: That makes sense. Just the
6 reason I actually asked that was because you had said
7 that if the *in vitro* or the clinical pharmacokinetic
8 studies show that a tablet can be compromised, then
9 there are the likeability studies, which implies that if
10 they don't show in either of those first two phases that
11 there's a potential problem. Likeability studies aren't
12 required or required or anything like that.

13 DR. HERTZ: We know that for the Schedule II
14 Opioids, there's a certain amount of likeability
15 associated with the drug substance.

16 So, we generally don't require that type of
17 study. If the goal of the development of a formulation
18 is, for instance, to avoid manipulation that can defeat
19 extended release characteristics and the formulation was
20 actually able to resist attempts to dose-dump, it still
21 has the abuse liability of the Schedule II Opioid.

22 So, we don't think it's not attractive or

1 likeable, but we know that it resists dose-dumping,
2 which can contribute to some of the morbidity and
3 mortality. The trouble is these are opioid analgesics,
4 so, they have to be able to deliver the opioid. So, no
5 matter what, an overdose is going to be possible, it's
6 going to be likable to some extent because it's got to
7 deliver the opioid in order to function as an analgesic.
8 And so, it depends on what the actual intent is and what
9 the results are. The reality is no product that we've
10 seen so far is completely capable of resisting
11 manipulation.

12 So, when it is manipulated, then the question
13 is how much do we need to know about what that does to
14 the likeability and that's when we start asking for
15 likeability studies.

16 DR. KIRSCH: We have three other people on the
17 list to ask questions, but we need to go on to the next
18 speaker, and I will start in order at our next question
19 period with Dr. Wolfe, Mendleson, and Omoigui.

20 So, we're going to go on to the next speaker,
21 who is Dr. Anthony.

22 **Data Resources and Metrics Used to Assess Prescription**

Opioid Misuse and Abuse

Designing Observational Studies on Drug Abuse

DR. ANTHONY: Good morning. I'm aware I stand between you and your break. So, I will move along. You can see I'm Professor of Epidemiology at several universities, as listed here, and I thank the FDA for inviting me to give this talk. I've been coming to advisory committee meetings for 35 years or more, and when they asked me to talk about this topic, I wondered whether there was anything I could say that the advisory committee wouldn't already have heard and why they needed me to say anything else.

And as we looked into the issue a little bit more, it turns out that my research group has been working on some population rate perspectives on evaluation of drug experience and that these were novel with respect to some ideas that have, perhaps, not previously been seen here.

So, what I'm going to do today is work around the topic I was requested to cover, mainly focusing on some conceptual issues and introducing some new ideas for evaluation in the post-marketing context. Most of

1 the drugs I've studied are not pharmaceuticals, and I'll
2 be giving you some examples outside the domain of
3 pharmaceuticals, but I think you'll be able to see how
4 the concepts and the research approaches can carry over
5 to the evaluation of products that at least where the
6 attempt is to improve patient safety.

7 I've given you an outline so you could see
8 where I'm headed. I'm not going to read through this
9 outline in the interest of time, but it's there just if
10 you'd like a roadmap of where I'm going.

11 The points of departure, I'm mindful that you
12 all are trying to focus on and clarify concepts and
13 approaches for risk management plans, and some of the
14 products that are to be evaluated have at least in
15 theory some safety advantages over already-marketed
16 products, but I also am mindful that there is a good bit
17 of knowledge and history and expertise in the room, and
18 there's no need for me to go over issues that have to do
19 with the basics of epidemiology and design of
20 observational studies in epidemiology as one might do
21 with a less-educated audience.

22 I'm going to focus on a Cross-Sectional

1 Approach that we are using mainly because that Cross-
2 Sectional Approach finesses some problems that have to
3 do with differential mortality. Mortality, for example,
4 that occurs quickly between the onset of drug use and a
5 follow-up at three, six, or one-year intervals, which is
6 the type of study that I've generally been doing over
7 the past three years. We find very often that the
8 people who are engaged in what would conform to the
9 current FDA definition of drug abuse often are not to be
10 found when we go to look for them in our follow-up
11 studies, and that's caused us, in part, to work on
12 Cross-Sectional Approaches. So, I'm going to focus on
13 that.

14 This will come as somewhat of a surprise to
15 those of you who have studied epidemiology because one
16 of the principles of basic epidemiology is that the
17 prospective and longitudinal design inherently is
18 superior to a cross-sectional design. That actually is
19 not always the case, and we'll see that in this context
20 it may not be the case.

21 I was asked to talk a little bit about
22 societal perspectives on drug abuse, and I have to say I

1 teach my trainees not to use the concept of drug abuse
2 because it's stigma-laden. In public health, we have to
3 pay attention to the communication value of the words
4 that we use, and it doesn't turn out to be very useful
5 to use the concept of drug abuse. So, we think of that
6 as a piece of baggage.

7 If you go back to Latin, the term impediment
8 is *impedimentum*. It's baggage that the Roman Army had
9 to carry along that kind of impeded their fast progress,
10 and abuse is a piece of baggage. We can reach inside
11 and pull out selected facets of abuse that can be
12 studied, but as a scientific concept and as an object of
13 study for an observational study, it probably is not
14 very helpful to us. Congress, however, is very fond of
15 it.

16 Same is true for abuse liability, but, here,
17 the problem is mainly that it conveys the idea that
18 abuse liability or dependence liability is a property of
19 the drug, and there are more productive ways of thinking
20 about becoming dependent or becoming a drug abuser if
21 you want to think about it that way, and I've sketched
22 one here on this slide.

1 So, in coverage of societal perspectives on
2 drug abuse, I think we have to realize that this is a
3 pejorative stigma-laden term, and it may be wise for us
4 not to think about abuse-deterrent products because it's
5 unlikely that any product is going to be deterrent of
6 abuse across all the range of facets of abuse that we
7 might be studying.

8 In my own work, I focus on drug dependence,
9 and a point of departures, this early study by L.
10 Lasagna in which he tried to find out what the response
11 of healthy volunteers would be to placebo and a profile
12 of other drugs, one of which was heroin.

13 What you can see here is that among 20 exposed
14 to heroin, 4 said they would have liked to repeat it and
15 70 of the 20 would not like to repeat it at all. So,
16 you can see that in contrast to the popular conception
17 about heroin, this isn't a drug that if you take it
18 once, you'll become hooked, and certainly that is true
19 of the marketed opioid analgesics that are in discussion
20 here.

21 Now, using that as a point of departure, in
22 our studies on drug dependence, which is not exactly the

1 same as wanting to repeat a drug experience, we focus on
2 a definition that has to do with three facets: One is a
3 disturbance of the mental life. This is where craving
4 comes into play. The only way we'd know about it is by
5 asking people about their mental life, and these are
6 obsession-like ruminations about the drug experience and
7 cravings.

8 Another domain of disturbance and dependence
9 running together with those in the mental life is
10 compulsion-like behavior. So, that here, something
11 manifest, you could actually see it. You wouldn't
12 necessarily have to ask about it, but it's like a
13 compulsion in psychiatry, and it may in some cases be a
14 compulsion. Its repetitions are rounds of drug-involved
15 behavior.

16 And then, finally, the third facet of this
17 syndrome is neuro-adaptation, as typically manifest in
18 tolerance, which might be subjectively felt or
19 demonstrated in the lab or a withdraw syndrome. So, if
20 you think about this syndrome definition, what we've
21 tried to do is ask how often people who use different
22 types of compounds develop this drug-dependent syndrome.

1 This is a summary of work that we've done.
2 We're updating these values with more recent data, but
3 we're not getting much change, and if we work our way
4 from the top to the bottom, if we look among people who
5 smoke tobacco cigarettes, even one cigarette, and ask
6 what proportion of them become dependent or develop a
7 dependent syndrome, as we've just defined it, it's about
8 one in three. If we do the same for heroin, it's about
9 one in four or five, and notice the similarity to the
10 Lasagna experimental evidence.

11 Going around the circle, you can see crack-
12 cocaine is followed by a crack-dependent syndrome
13 slightly more often than cocaine-hydrochloride powders,
14 followed by a cocaine-dependent syndrome. And we can
15 work our way around to the opioid analgesic drugs to
16 about 1 in 11.

17 I should note here that the context is
18 extra-medical use. This is not a medically-prescribed
19 user. I think the values would be much smaller if we
20 were to include in the denominators people who are
21 getting these medicines from the doctor in a prescribed
22 context, such as a pain management clinic.

1 These are people who will acknowledge to us
2 that they've used it outside the boundaries of what's
3 been prescribed either for feelings that it produces or
4 they've taken it for reasons the doctor didn't prescribe
5 it. So, they might have gotten a pain medicine after
6 foot surgery, and they woke up in the morning and felt a
7 hangover after heavy drinking and took the medicine to
8 help relieve that hangover. That would count as extra-
9 medical use, and we're including those people in these
10 denominators. We're not including people who are taking
11 the medicine as the prescriber intended.

12 So, these are the relative proportions that we
13 get when we go out into the population and accumulate
14 over the experiences of drug-users drug-by-drug, looking
15 at each form of the dependent syndrome.

16 In terms of the design, you're going to hear
17 more about this because the National Surveys on Drug Use
18 and Health, which will be discussed next, is often a
19 source of data for our studies. Typically, these are
20 pre-designated U.S. population studies. We're now
21 working in 22 different countries. So, we should have
22 estimates for other countries before too long. We have

1 multi-stage area probability sampling of dwelling units,
2 and then probability sampling of the respondents. We
3 recruit with IRB-approved protocols. There are
4 standardized assessments that are either anonymous or
5 confidential. Nowadays, they tend to be
6 computer-assisted self interviews or personal
7 interviews. The assessments include standardized,
8 prewritten items, and routing patterns, branching
9 patterns through the assessments so that we can follow-
10 up and give details about experiences as they're
11 expressed.

12 For the drug-dependent syndrome, we have what
13 we call testlets, each facet of the syndrome is
14 evaluated with multiple items. We then estimate
15 cumulative incidence proportions for each drug group,
16 and we pay attention to variants in the constraints.

17 Now, one of the questions that was raised in
18 pre-discussions of this talk is whether there process
19 phenotypes on the way to the full dependent syndrome
20 that might be investigated in the marketing of new
21 products, and the answer is yes, there are, and I'm
22 going to focus for the next few minutes on that topic.

1 They typically are going to require fairly large samples
2 to identify them.

3 The idea of the process phenotype can be seen
4 in this graphic. It's a stage transition model. At
5 number one, you see the onset of drug use. At number
6 two, a building up of count of drug experiences for
7 those who use the drug more than once. Number three,
8 sometimes after repeated drug experience, you'll get the
9 formation of the clinical features that I described
10 earlier, the craving, the ruminations, the compulsive-
11 like behavior, and so on. And then, number four, that
12 those features can coalesce into a syndrome which we
13 would call the drug-dependent syndrome. And then, at
14 number five, there could be secondary complications of
15 that syndrome.

16 Now, of course, there is potential cessation
17 of use at each step, and one of the questions is how
18 many people use the drug once and then will continue to
19 use the drug and how many people are not likely to use
20 it again? This brings us to the concept of a population
21 rate perspective on drug abuse as opposed to the
22 individual risk perspective. The heritage of this

1 concept goes back to an early geneticist, Wilhelm
2 Johannsen, who coined the terms "genotype" and
3 "phenotype," and most of the time nowadays, because of
4 prominence of molecular genetics and biology, we think
5 about the individual type of genotypes and phenotypes.
6 Johannsen thought more broadly, and he thought about a
7 population perspective on phenotypes and thought of them
8 as population characteristics.

9 A related idea was introduced more recently by
10 Epidemiologist Rose, who drew distinctions between
11 causes of incense and causes of cases.

12 In the interest of time, I'm not going to be
13 able to say much about this, except I'm going to
14 illustrate with an example that has to do with drug
15 dependence, and you have the references here if you're
16 interested in that.

17 If you want to think about this idea of the
18 process phenotype, you can think about a population that
19 studied from birth to death. Some of them try a drug or
20 take a marketed product one time, never repeat it again.
21 Others will repeat it. Sometimes this will happen
22 quickly after the first try, which could be a

1 manifestation of liability to dependence, or it could
2 happen after a lengthy lag interval.

3 If we observe these people longitudinally to
4 death, we can know the count and lag times of these drug
5 experiences, but in a cross-sectional survey, we cannot
6 know. We take a slice in time and we'd see whether
7 someone was recently using the drug, but we wouldn't
8 know among those who were not using it whether they
9 would ever use it again.

10 Well, if we set up the problem appropriately,
11 we actually can estimate those who would never use it
12 again not at the individual level, but at the subgroup
13 level, and if we think about ethanol as a drug
14 understudy and if we were to take into account potential
15 protection, and here, I'm thinking of the protection
16 that you might like to have in a so-called abuse-
17 deterrent formulation, what we would expect to see with
18 respect to ethanol is that in population subgroups that
19 have an excess prevalence of a null variant of liver
20 metabolizing enzyme alleles, we would have less
21 likelihood to become dependent upon that drug, and this
22 should be manifest in a process phenotype that shows up

1 very soon after the onset of the drug, and this is where
2 I think these ideas might be portable to the context of
3 post-marketing surveillance of new products where the
4 goal is to try to confer some protection by virtue of
5 the product characteristic. Here, the protection we're
6 hypothesizing has to do with genetic variation and
7 responses to ethanol.

8 So, I can't point to any Asian-American in a
9 cross-sectional sample and declare whether this person
10 might be in the future a persistent drinker or never
11 again drink, but if I look at the Asian-Americans who
12 very recently have started to drink and I ask whether in
13 the most recent interval of time, say 30 days, whether
14 they have had even one drink and then what is the rate
15 of drinking in those 30 days, I then can estimate
16 whether Asian-Americans are over or under-represented in
17 a group of people who are not likely to drink, again,
18 versus those who are likely to drink again. I can also
19 estimate the rate of drinking conditional on the
20 membership in these classes.

21 And what you can see here in data that are
22 just submitted, the PP is the persistence parameter of

1 this regression model, and we get an inverse
2 association, non-Hispanic, Asian-Americans compared to
3 non-Hispanic whites are less likely to persist in their
4 use of ethanol, and we hypothesize this is related to
5 the pharmacokinetic substrate. I'll come back to that
6 later.

7 The RR parameter is the rate ratio, so,
8 conditional upon membership in the persistent drinking
9 or using class, we have a negative sign; the rate for
10 the Asian-Americans is lower than the rate for whites.
11 And so, here we're seeing before anyone has developed an
12 alcohol-dependent syndrome or actually a few of these
13 individuals will have developed it, but even if we set
14 aside the alcohol-dependent individuals, we can see a
15 subgroup in which there is an apparent protection
16 against the risk of becoming drug-dependent.

17 In theory then, in terms of post-marketing
18 surveillance, this type of approach could be used within
19 12 to 24 months of release of the drug in order to see
20 if, in fact, we would see manifestations of reduced risk
21 of these process phenotypes.

22 We don't find these relationships for Asian-

1 Americans for tobacco, cocaine, or cannabis. We're now
2 studying them for opioid analgesic compounds, but I'm
3 not ready to report that yet.

4 Now, I will show you some process phenotypes
5 that have to do with the opioid analgesic drugs, and
6 this may overlap a little bit with a talk that'll be
7 given later on, but these process phenotypes are the
8 actual clinical features of drug dependence, and they're
9 listed here.

10 So, without asking who has developed the drug-
11 dependent syndrome, we can ask about the accumulative
12 incidents soon after onset of use of each of these
13 clinical features of drug dependents as steps on the way
14 to the full phenotype.

15 Here, the subgroups under study are kids,
16 adolescent onset drug-users, kids who start using these
17 drugs; in this case, it's opioid analgesics, before age
18 18, and the contrast group is those who start as young
19 adults or a little later. Most of them are 18 to 25.
20 And what you can see, if we look across the profile of
21 these process phenotypes, at the individual clinical
22 features of dependence, among people with or without

1 respect to whether they're become dependent, we see five
2 aspects where the adolescent onset kids seemed to be at
3 greater risk. One is getting over the effects of the
4 drugs, spending a lot of time getting over the effects
5 of the drug, needing more drugs to take to get the same
6 effect, having emotional problems connected with their
7 drug use, reducing other activities, non-drug
8 activities, in order to use drugs, and then having
9 withdrawal experiences.

10 So, this would be another example of a
11 phenomenon of drug dependence related to drug
12 dependence, but not the full dependent syndrome that
13 could be studied in the post-marketing context within 12
14 to 24 months after onset of use. We're actually
15 estimating these parameters for a lag time of 180 days
16 elapsed since first use of the drug. So, we could get
17 data in a fairly timely fashion via cross-sectional
18 surveys on these topics.

19 And then, I'm here just going to contrast
20 male/female differences, and here, we're looking at the
21 newly incident opioid analgesic users using outside the
22 context of medical practice. They're about half and

1 half male and female, and what you can see here on the
2 left of the gray bars for males and females combined,
3 the white bar, you can't see very well, but it's the one
4 in the middle is for males and the yellow bar is for
5 females. Here, you can see that, in general, females
6 are more likely to develop these clinical features.
7 There's one exception of the set. And again, you can
8 see how this type of approach, evaluated within 12 to 24
9 months after onset of the use of the drug can be used to
10 study steps on the way to becoming drug-dependent.

11 Now, in all of these studies, there's a need
12 to pay attention to potentially confounding variables.
13 If you consider the Asian-American example, we're
14 hypothesizing a protection based on a null variance of
15 the alleles, but Asian-Americans are different from
16 other parts of the population in other ways. There's
17 often more family cohesion, more family attention,
18 parental monitoring, and the like, and those would have
19 to be taken into account before we could attribute the
20 protection to one factor or another.

21 I do want to note though that in this context,
22 there is a potential for over-control of what is

1 suspected as a confounding variable. So, if someone
2 says well, why don't you control for school dropout or
3 income levels, well, those may be responses to the drug
4 use.

5 I made some notes for future directions, but I
6 want to turn the time over to you for questions, and if
7 anyone wants to talk about these issues, I'd be happy to
8 talk about them. The one point that I was encouraged to
9 emphasize is that there are other domains of
10 pharmaceutical products where, in theory, manufacturers
11 are trying to improve the safety profiles, and we're not
12 just talking about FDA, but also about other devices,
13 other consumer commodities. And it may be that it's
14 useful to look outside of the narrow boundary of the
15 drugs that we pay attention to in this advisory
16 committee in order to borrow some experience.

17 Now, the Energy Department, for example, is
18 asking for some evidence of the firm's financial
19 capacities to deal with the damage if something happens
20 in offshore oil drilling. We could think of collective
21 insurance plans in order to protect the society and the
22 firms against a potential hazard or catastrophe with a

1 product that, from a theoretical and pre-marketing point
2 of view, looks like it has advantages. I hope that that
3 perspective is brought to bear in the advisory
4 committee's work on these problems. The tendency may be
5 to block out the gate and not let any new products out
6 because we're worried about a repetition of past
7 experiences, but the American public needs products and
8 needs innovations that are trying to improve safety of
9 these products, and we may need to look outside narrow
10 boundaries of abuse context in order to borrow from
11 other domains of FDA or federal government regulation.

12 Thank you very much.

13 DR. KIRSCH: Thank you. Before you leave the
14 podium, can I assume that you'll be here throughout the
15 day?

16 DR. ANTHONY: Yes.

17 DR. KIRSCH: So that at the question period,
18 you'll be able to answer questions?

19 DR. ANTHONY: Yes.

20 DR. KIRSCH: Okay. So, with that, we're going
21 to take a break. The break is going to be 15 minutes in
22 duration. Committee members, please remember that there

1 should be no discussion of the meeting topic during the
2 break amongst yourselves or with any other member of the
3 audience. And we will resume at 10:32.

4 (Break.)

5 DR. KIRSCH: While you are taking your seats,
6 I will ask our next speaker, Dr. Woodward, to approach
7 the podium, please.

8 (Pause.)

9 DR. KIRSCH: Okay. Dr. Woodward?

10 **Substance Abuse and Mental Health Services**

11 **Administration: Resources and Methods**

12 DR. WOODWARD: First of all, thank you for
13 inviting me to talk briefly about the datasets that are
14 of interest to FDA and the field.

15 CBHSQ is an acronym you may not be familiar
16 with. It's the Center for Behavioral Health Statistics
17 and Quality. You may be more familiar with the old
18 Office of Applied Studies. The name was changed in
19 July, and I'll explain a little bit more about that in a
20 second.

21 I have no conflicts of interest being a good
22 government bureaucrat, keeping my head as low as I can.

1 Let's see. The Center has more
2 responsibilities than the old office did, but I'm not
3 going to be talking about the new responsibilities; I'm
4 going to be talking about the three main datasets that
5 the CBHSQ, or, if we had IT would be CBHSQIT, has, and
6 they were consistent with the Office of Applied Studies.
7 There are three main datasets, the National Survey of
8 Drug Use and Health, the Treatment Episode Dataset, and,
9 finally, the Drug Abuse Warning Network that I'll talk
10 about. I'm going to give a very high-level, 10,000 foot
11 view of the datasets, given the time that I've got.

12 The first is the National Survey on Drug Use
13 and Health, as you can see from the slide; these are the
14 main features of the dataset. It's an interview of
15 about 68,000 people per year. It takes an hour, it's
16 very detailed, it's computer-assisted so that we're able
17 to provide the questionnaire in a number of different
18 languages. It's only for people over the age of 12.
19 So, there's a component of the population we don't
20 capture in the NSDUH that's of interest to this field so
21 that we're able to present prevalence/incidence data for
22 the nation and in each of the states. In each state, we

1 can provide direct estimates. The others are indirectly
2 estimated.

3 There are two main changes of historical note.
4 In 1999, the computer-assisted approach was used so that
5 produced a break in the trend. 2002, we introduced a
6 payment of \$30 per individual, and both times, the
7 prevalence went up, the response rate improved.

8 The overall response rate for this large a
9 survey is just about 70 percent, which we'd like to
10 improve, but given how difficult it is to collect survey
11 information these days, it's pretty sound.

12 The household survey started out with an
13 emphasis on illicit drug use. So, what I wanted to do
14 is to just briefly review the kinds of information
15 that's collected. So, including both with illicit drug
16 use and non-medical use of prescription drugs, there's
17 recency of use, frequency of use as much as daily so
18 that we can report on, say, somebody who uses every day
19 in a given year. The initiation data for particular
20 drugs are captured. Dependence and abuse resulting from
21 drug use is captured in the diagnostic, statistical,
22 manual criteria. Also, we collect whether or not

1 treatments received is the result of a particular
2 problem.

3 As far as prescription drugs, the strategy of
4 the NSDUH is to try to report on the four major
5 categories of drugs: therapeutic classed as a pain-
6 reliever, stimulants, sedatives, and tranquilizers.
7 There is information collected on specific
8 pharmaceuticals, including brand names and generic
9 drugs. What the respondent gets is a set of
10 photographs, what we call pill cards, showing each of
11 the drugs by their categories. They report what they
12 have. If they don't see anything, they can type in
13 other drugs.

14 The reporting of the drugs is largely
15 aggregated at the therapeutic class level. Right now,
16 the NSDUH is trying to improve the definition of drugs
17 of what is considered drug use so that we won't really
18 be able to collect information on dose, but we will be
19 able to get a better sense of the type of use, whether
20 it's over medication or misuse. Right now, the NSDUH
21 really can't distinguish very well in that area.

22 The second major dataset that I want to talk

1 about is the Treatment Episode Dataset. It's part of
2 larger data collection system called the Drug and
3 Alcohol Services Information System, DASIS, which has
4 some other components with it. This is an
5 administrative dataset that states report to our office.
6 We crosswalk the data to make sure there's consistency
7 in what we collect from the data. It's an episode data
8 system, very few states collect individual patient
9 identifiers.

10 So, we can't really track patients very well.
11 Most of it is treatment admission data. We do collect
12 some discharge data. A lot of the states are now
13 reporting discharge information.

14 It's facilities that the states keep track of,
15 and these are largely public-funded, specialty treatment
16 facilities or clinics, if you will. And there are
17 something like 13,000 of them throughout the nation. Of
18 course, with the economic downturn, there are fewer.
19 We estimate that we're picking up about 80 percent of
20 the facilities. We don't have the private-funded
21 facilities, as much information on them. And there are
22 slightly under 2 million admissions every year.

1 The information that's collected, as you can
2 see, our demographic variables, the discharge dataset
3 includes some socioeconomic information, employment
4 history, and insurance coverage. There is a link
5 between admissions and discharge records.

6 So, the information in the state report is the
7 three main substances, at admission, route of
8 administration, how the drug's taken, frequency of use,
9 age at first use. Treatment variables largely focus on
10 the type of treatment, where the individual's going.
11 There is some limited information on treatment outcomes,
12 length of stay. So, this particular database isn't as
13 useful, if you will, for the field because there isn't
14 really information collected on brand names or
15 formulations. It's general. There are groupings that
16 we can't really disaggregate further.

17 For example, opiates are aggregated into a
18 class, and we can't really drill down further, if you
19 will. In a minority of states, 16 report on opioid
20 analgesics. So, it's probably a limited use to this
21 field.

22 The last dataset I want to touch on briefly is

1 the Drug Abuse Warning Network, which has been around,
2 like the NSDUH, for quite awhile. Initially, the intent
3 was to design a sentinel public health surveillance
4 system. It's now sort of focused on nationally public
5 health problems that are captured in emergency
6 departments throughout the nation.

7 The information is collected by trained
8 recorders who go to about 250 hospitals throughout the
9 nation. Some of the hospitals have their own recorders
10 who are also trained to report the data that we collect
11 directly from the hospital emergency record. And what
12 we focus on, it's a fairly short data collection form
13 with about 20 data elements. It is where an ED visit
14 has drugs reported either as a direct cause or
15 contributing factor, either determined from toxicology
16 records or what's in the notes in the reports from the
17 medical record.

18 There are about 4 million drug-related visits
19 that we capture each year. That's out of about 110
20 million ED visits throughout the nation. So, it's about
21 4 percent. So, as you can imagine, it takes a lot of
22 effort to try to get to that 4 percent in terms of

1 screening.

2 What we do is to select a representative group
3 of EDs throughout the hospital. The criteria for
4 inclusion is short-term, general, non-federal hospitals
5 with 24-hour emergency departments. We over-select for
6 12 metro areas, and we have a remainder sample of
7 hospital EDs so that we can, along with the metro areas,
8 provide nationally representative information for the
9 country.

10 Now, the estimates include the usual
11 statistical adjustments for sample design. The biggest
12 strata size is the most important. Strata size is
13 hospitals where we don't have data reporting. They're
14 adjusted for if the hospitals don't report for a full
15 year, we make adjustments for that. We also have
16 introduced one in three sub-sampling; that is every
17 third ED record is reviewed or screened. And that's
18 simply so that we can save costs without sacrificing
19 efficiency. There isn't much increase in bias when we
20 do that.

21 This gives a sense of the information that we
22 collect, how it breaks out for use in analysis. In the

1 left, you can see pharmaceuticals under "medical use."
2 This represents the adverse effects that we can pick up.
3 Non-medical use can be broken into pharmaceuticals,
4 illicit drugs, and alcohol. For alcohol, I need to
5 clarify that if the only drug onboard, if you will, that
6 is associated with the ED visit for somebody under the
7 age of 21, we don't have any age restrictions as the
8 NSDUH does. We capture that, but if the individual is
9 over 21, we only capture alcohol if there are other
10 drugs present. In alcohol for somebody under 21 is
11 basically an illicit drug.

12 Non-medical use is defined, as you can see,
13 exceeded prescribed or recommended doses. Somebody
14 using a particular drug when it was prescribed for
15 somebody else. An intentional poisoning, intentional
16 administration of a drug to somebody intentionally, as
17 well as any substance abuse that we pick up from the
18 medical record. We exclude suicide attempts and the
19 non-medical use, and we include suicide thought and
20 plans.

21 Finally, for the DAWN, the value of the DAWN
22 to the field is that it provides detailed brand level

1 specific drug information at the ED visit, which is
2 important because any ED visit where there are drugs as
3 a part of the visit indicate a fairly serious
4 consequence.

5 We aren't able to collect dose and source of
6 drug. As you can imagine, it's very difficult to
7 collect that information if the patient really isn't
8 fully conscious. Oftentimes, patients, they aren't able
9 to provide that. If they bring in a bottle, they may
10 know how much they've taken, but, oftentimes, they
11 don't.

12 The ED record often doesn't have enough
13 specificity for the recorder to enter the detail level
14 of information that we would like to collect. So,
15 often, there's some ambiguity. By and large, I think
16 the databases -- most of the drugs reported are fairly
17 well documented. We used the Multum Lexicon which we
18 adjust for street level names, and we use that to try to
19 get to as great a specificity and the types of drugs
20 that are included in the ED visit.

21 If you want to find out more, you can go to
22 the Web Site under the old OAS. The Web Site, we're

1 trying to improve it. But it will provide a wealth of
2 information and various publications.

3 We have public use files for the NSDUH and for
4 the TEDS under SAMHDA. That's the Substance Abuse
5 Mental Health Data Archive. It's part of ICPS, our
6 University of Michigan public data file archives, and
7 it's a very powerful source of information. You can
8 build your own tables, download your own files, and do a
9 certain amount of statistical analysis, variance
10 calculations, regressions with the SAMHDA. We're trying
11 to put the more current DAWN information on there, and
12 we hope to have that public use files, data tables ready
13 in the next few months.

14 Finally, I just wanted to say that we are
15 working with FDA through an interagency agreement to
16 provide data requests. Sometimes, our office feels as
17 if we're subcontractor to FDA to try to answer specific
18 requests. So, we've set up an interagency agreement to
19 try to extend our limited staff resources, and we have
20 been working with FDA to make them understand to make
21 sure that we comply with the federal privacy and
22 confidentiality laws. Even though we don't collect any

1 information that's directly identifiable, that is where
2 there's personal health information collected, we are
3 aware that through triangulation and other data sources
4 it may be possible to identify individuals, which is
5 against every federal law dealing in that area. So,
6 we're very careful about that.

7 And that's it. It's a very high-level level,
8 and, so, once again, thank you for allowing me to talk.

9 DR. KIRSCH: Thank you. Our next speaker is
10 Dr. Dormitzer.

11 **Available Data Resources to Assist in Measuring Abuse**
12 **Behaviors, Patterns, and Outcomes**

13 DR. DORTMITZER: Hi, good morning. My name is
14 Cathy Dormitzer. I'm an epidemiologist in the Division
15 of Epidemiology in the Office of Surveillance and
16 Epidemiology. I will start with a brief background.
17 I'll present standard data sources, both public and
18 proprietary for numerator and denominator data. I will
19 give a brief description of the Prescription Drug
20 Monitoring Programs, and then finish with a summary of
21 the challenges with the current data sources.

22 But, first, what are numerators and

1 denominators, and why do we need them? Well, numerators
2 measure outcomes. So, in absolute numbers, what are the
3 numbers of events of interest, and denominators provide
4 some context of the burdens of these outcomes.

5 These are a few data sources that contain
6 information on -- there are very few data sources that
7 contain information on both numerator and denominator
8 information and are actually able to link them. So, we
9 use both numerator and denominator sources of data.

10 So, the data sources presented are ones that
11 measure events related to drug misuse and abuse. They
12 are reports on the non-medical use of drugs, events such
13 as emergency room visits, and outcomes such as drug
14 dependence or drug-related deaths. In the past, these
15 measures of misuse and abuse were mainly used for
16 illegal drugs, but now we are using these same data
17 sources for prescription drugs that are approved and
18 regulated by the FDA.

19 So, standard data sources, most of them are
20 nationally representative, usually multi-stage
21 probability sample. There are data sources that have
22 been used for many years, and they've also been

1 presented both by Dr. Woodward and by Dr. Paulozzi.

2 It's not exhaustive. It does include the
3 sources that FDA has used in the past though, and we use
4 them to examine drug abuse outcomes.

5 So, as you can see from the list, half of them
6 are funded by SAMHSA and were previously presented by
7 Dr. Woodward. They are sources of numerator data. So,
8 the number of events related to misuse, abuse, and
9 related outcomes, and all of these are publicly-funded
10 data sources.

11 So, DAWN provides national estimates of drug-
12 related emergency room visits, and they also provide it
13 as numbers per 100,000. And particularly important are
14 the SAMSHA-defined constructs of non-medical use of
15 pharmaceuticals that Dr. Woodward related to, and they
16 are the cases that are classified as over-medication and
17 other, as well as malicious poisoning, but malicious
18 poisoning is usually very low. But they are considered
19 abuse-related, and, so, that's called NMUP. And then,
20 in addition to NMUP, there's also ALLMA, which are all
21 the NMUP cases plus ED visits where alcohol or illegal
22 drugs were present in the patient. And FDA also

1 examines DAWN medical examiner data. Now, these data
2 are not nationally representative, but they do provide
3 data on a consistent panel of medical examiners on a
4 number of drug-related deaths.

5 And the strengths of DAWN are that it is
6 nationally representative. And we do have data that's
7 specific to substance, formulation, and sometimes even
8 brand. And it's very limited, but there is also data on
9 route of administration, but it's very limited.

10 Now, the limitations of these data is that
11 there is lag time because national estimates are
12 generally not available until 9 or 10 months after the
13 end of the calendar year from which the data is
14 produced, and ME data did not provide information on
15 drug formulation, and it's also not nationally
16 representative.

17 And the last important limitation of DAWN data
18 is that it provides data on misuse and abuse that
19 resulted in a medical outcome, either an ED visit or a
20 death, not on the behaviors.

21 The National Survey on Drug Use and Health
22 does collect data on drug abuse behaviors, and the

1 questions are taking the drug not prescribed for you or
2 just for the feeling it caused? Now, it does ask these
3 questions on prescription drugs, but it's pain-
4 relievers, tranquilizers, stimulants, and sedatives.

5 And notice the strengths are that it collects
6 data on behaviors. So, we're interested in that. And
7 it collects it directly from the respondents, and it's
8 behaviors that may not have resulted in a medical event.
9 The limitations are that it's got the same nine-month
10 lag time and that it focuses on drug classes. So, it's
11 pain-relievers, not specific opiates, although there are
12 questions that were added for OxyContin in 2002.

13 The last SAMHSA dataset I'll be discussing is
14 TEDS, and it collects data on the number and
15 characteristics of a person's admittance to substance
16 abuse treatment program. So, we do get information on
17 the top three substances of abuse at the time of
18 admission. We get information on route of
19 administration, as well as frequency of use and age of
20 first use.

21 And the strengths of TEDS are that it collects
22 data on drug substance, but it's fairly limited in terms

1 of classes. So, it's not always very specific, and it
2 also does provide some insight on the public health
3 burden on opioid analgesics.

4 The limitations are that these data are not
5 always completely nationally representative, and that
6 fact that 16 states report on specific opiates, but the
7 rest don't.

8 Now, Monitoring the Future, which is conducted
9 by the Institute for Social Research at the University
10 of Michigan, and it's funded by NIDA, which is the
11 National Institutes on Drug Abuse, is an in-school
12 survey of drug abuse behaviors, attitudes, and values of
13 high school and college students, as well as young
14 adults, and it includes questions on attitudes and
15 perceived harmfulness of prescription drugs, including
16 opiates.

17 The strengths on Monitoring the Future are
18 that it examines drug abuse behaviors among a population
19 that's usually recently begun to start using and abusing
20 drugs. It's nationally representative, and it's been
21 conducted over many years.

22 The limitations are that respondents are asked

1 on their use for drug classes, such as sedatives,
2 amphetamines, or narcotics other than heroin, not on
3 specific drugs, formulations, or brands. But they are
4 asked on Vicodin and OxyContin, and usually adolescents
5 really can't distinguish between brand or generic. So,
6 it's not a perfect measure. And it only collects data
7 on youth that attend school.

8 The Adverse Event Reporting System is a
9 database of FDA's Post Market Safety Surveillance
10 Program for all approved drugs. And it's used to
11 monitor adverse events and medication errors that might
12 occur with these products. It's voluntary and receives
13 some adverse event and medical error reports directly
14 from health care professionals and consumers, but
15 manufacturers, by regulation, are required to send these
16 reports to FDA.

17 And the strengths of AERS is that it can
18 provide information on signals related to drug misuse,
19 abuse, and dependence, but it's not complete reporting.
20 In fact, there is substantial underreporting, so, it
21 cannot be used as a surveillance tool.

22 Dr. Paulozzi actually cited most of these

1 datasets, but he also presented data on overdose deaths
2 involving opioid analgesics from the National Vital
3 Statistics. It's data extracted from death
4 certificates, and it includes information on all deaths
5 in the United States.

6 And the strengths of these data are these data
7 are not a sample. It is the true population. But the
8 limitations are that it provides data on opiates as a
9 class except for methadone, and that the data are
10 usually available a few years after the calendar year
11 has ended. So, that's another long lag time.

12 Now, I will discuss data sources that are
13 proprietary data sources, and these are just some
14 examples. Some are newer, may use different sources of
15 information, such as the Internet. Some may not be
16 nationally-representative, although they are increasing
17 their coverage. And since these data sources are part
18 of both Sponsors' proposals, they will be probably
19 giving more detailed prescriptions. So, again, I'm
20 going to be brief.

21 NPDS, which is the National Poison Data
22 System, provides data on poison exposure phone calls

1 into poison control centers. They collect calls from
2 poison control centers across the United States, and
3 includes both calls on drug exposure as well as calls on
4 information for specific drugs.

5 It is a large data source, and it can provide
6 some data that is specific, even down to the level of
7 formulation and sometimes brand, but this information is
8 limited, and there is lag time for the annual reports.

9 RADARS was developed in 2002 by Purdue, but in
10 January of 2006, RADARS became a non-profit and
11 operation administered by the Rocky Mountain Poison and
12 Drug Center, and a representative from RADAR will be
13 presenting today, so, I'm not going to go into the
14 details of these data. But one strength of RADARS is
15 that it does provide timely data that can be brand-
16 specific, it's published their findings in numerous peer
17 review journals so others in the research community have
18 reviewed their work, and that's also true for actually
19 most of the datasets. And one limitation is not all
20 components of their data are nationally representative.

21 NAVIPPRO is a system that collects information
22 on prescription opioid abuse, and it's also included in

1 the Sponsor's proposal, so, I'm not going to be
2 providing a lot of detail.

3 One of their strengths is also a limitation
4 because they gather a great deal of detailed information
5 from people seeking treatment for their drug dependence.
6 So, these are people who actually have quite a bit of
7 knowledge about the abuse of opiates, and that provides
8 information, and that's probably, like I said, their
9 biggest strength and their biggest limitation, but that
10 might not be generalize-able to the population as a
11 whole.

12 So, now I will present denominator data. When
13 providing the number of drug abuse events, the default
14 denominator is the U.S. population. And these data can
15 be refined by getting the number of events per 100,000
16 population, by age group, as well as the geographic
17 region, such as state or ZIP code. We can also get
18 information from the amount of drug utilization either
19 from ARCOS, which is the Automation of Reports
20 Consolidated Order System, which is ARCOS, and that's
21 administered by the EA, and that was also presented by
22 Dr. Paulozzi. But FDA also purchases excess to drug

1 utilization data sources.

2 So, the U.S. Census data is readily available,
3 it's easily understood, and it provides data on the
4 public health burden of these events and provides data
5 on groups that are at risk. It does not, however,
6 provide data on drug utilization. Drug utilization can
7 be considered exposure; how much of the population is
8 exposed to the drugs that are being examined.

9 So, ARCOS, which is DEA's dataset, it tracks
10 all schedule drugs that are in Schedules I, those are
11 the illegal drugs, and II, and both morphine and
12 oxycodone are C2s, as well as all narcotics from all the
13 schedules. And opiates are considered narcotics, so,
14 all levels. And it is from the point of manufacturer to
15 the time they are delivered to the pharmacies. For the
16 most part, it reports the number in kilograms sold by
17 drug. This system also has some information on
18 formulation and substance.

19 This is not a projection. This is all drugs
20 sold. The limitation is that it does not provide
21 information on the numbers of prescriptions sold. So,
22 it's once it's reached the pharmacy, we don't have any

1 further information with this data source.

2 So, FDA has purchased access to many data
3 resources that provide estimates on the amount of drug
4 sold by substance, formulation, and brand, and this is
5 detailed information that includes data on the
6 prescriber, the patient, and the indication for which
7 the drugs are prescribed. And it also provides
8 information on concurrent use of multiple drugs.

9 So, these data are used as denominators, and
10 it does put drug abuse events into context. And we use
11 these data to assess the amount of risk within the U.S.
12 population. We are also using these data to understand
13 drug-prescribing patterns and abuse, and, also, we use
14 it to assess risk management, plans, and practices such
15 as labeling.

16 So, it does provide very specific information
17 on substance formulation and brand. The limitations are
18 that they are projections. It is not the amount sold.
19 And we still don't know how the drug is taken by the
20 individual patient. The patient may have left the drug
21 in their medicine cabinet and that could have resulted
22 in a family member taking it, or they could have sold

1 it. And all we need to keep in mind that these data are
2 in no way linked to the outcomes associated with drug
3 abuse.

4 Okay, now I will discuss the Prescription Drug
5 Monitoring Plans, which are the PDMPs. And PDMPs are
6 statewide electronic databases that collect data on
7 controlled substances that are dispensed in pharmacies
8 by state. They were first started in 2002, and there
9 are currently 34 states that receive federal funding.
10 And there are two federal funding sources for the PDMPs.
11 The first is the Harold Rogers Prescription Monitoring
12 Plan, and that's administered by the Department of
13 Justice. The second source is NASPERA, which is the
14 National All Schedules Prescription Electronic Reporting
15 Act administered by HHS, the Department of Health and
16 Human Services. And this program enables states to
17 create PDMPs or enhance existing ones.

18 And these programs were just started, they're
19 very new, and they were started to make sure that there
20 was access to legitimate drugs that work, controlled
21 substances, and, at the same time, identify people that
22 have multiple prescriptions for the same substance, and

1 to intervene and offer treatment for people who are
2 addicted to prescription drugs. It also provides data
3 for finding drug abuse trends. It also began to address
4 the issue around doctor shoppers. So, doctor shoppers
5 are someone may go to different physicians to get the
6 same prescription multiple times for drug abuse
7 purposes.

8 And FDA can use these data in a few different
9 ways to identify which drug substances and formulations
10 are targeted by doctor shoppers. The data though are
11 still very new, understand development, so, they
12 continue to evolve and change. And, to data, not all
13 states have PDMPs. So, that's still a challenge. And
14 we are still learning how to use this data.

15 So, in conclusion, as we think about all these
16 data sources and how we will use them, we are faced with
17 the challenges that new drugs and formulations that
18 address the issues associated with drug abuse are
19 currently being developed or are currently under review.
20 And when we're looking at new ways to evaluate these
21 abuse-deterrent formulations, we are using current and
22 new data sources, which are just being developed, and

1 how these data sources will be used to sustain a
2 labeling claim of abuse deterrence is something that
3 we're working very hard on.

4 Thank you.

5 DR. KIRSCH: Thank you.

6 We're now going to go to the question and
7 answer session again. Our first question will be given
8 by Dr. Wolfe.

9 **Clarifying Questions**

10 DR. WOLFE: I was out of the country in
11 September of 2009, when these committees met to decide
12 whether or not there was enough evidence of some
13 improvement with OxyContin in the formulation to go
14 forward. And so, I read the transcript of this meeting
15 yesterday just to see what happened, and there were a
16 few people, including Dr. Flick, Dr. Kirsch, who were
17 concerned about going ahead, and I'll just quote this
18 because it's a comment and I have a question afterwards.
19 Dr. Kirsch voted against this because he said it's
20 "unconscionable to move forward without well-defined
21 REMS." I am mainly an optimist, and I think that one of
22 the purposes of this meeting today and tomorrow is so

1 that the next time one of these drugs comes forward,
2 there will be a REMS at the beginning rather than a year
3 later.

4 But I want to move back one step and ask
5 questions of really the speakers this morning. as you
6 look at the submitted ideas for epidemiological studies
7 by the company, FDA's ideas, and so forth, are there not
8 some of these studies that could be done prior to
9 approval? I mean, when you're sort of struggling for a
10 comparator group and knowing that OxyContin old is not
11 around anymore, is it not possible to--I mean, I am all
12 in favor of post-market surveillance. It's necessary,
13 and a lot of these databases need to be utilized. But,
14 so, my question is to any of these people who spoke this
15 morning.

16 Can you see any studies that could be done
17 prior to approval or more definitively answer the
18 question of whether there is a reduction in abuse
19 potential. Again, OxyContin, but the same is true for
20 Embeda before naltrexone was embedded in it. It did not
21 have naltrexone, and the comparison would be useful.
22 That's really the question open to anyone who spoke.

1 Any kinds of studies, whether it's using these processes
2 phenotypes that Dr. Anthony described or any other
3 means? Cross-sectional studies. Anything that could be
4 done prior to approval so we'd have a better idea about
5 whether there appears to be a risk reduction, as not to
6 say that you still don't need the post-marketing
7 studies.

8 DR. KIRSCH: Dr. Rappaport, would you like to
9 take that question or appoint it to somebody?

10 (Laughter.)

11 DR. RAPPAPORT: Well, I can try to speak to
12 some of it, perhaps. I think there may be components,
13 as you mentioned, if there's baseline work or comparator
14 work that could be done prior to approval, and then once
15 a drug gets on the market, we could do those
16 comparisons, but I think we'd have to be careful about
17 secular trends. I think Dr. Lapteva pointed out that
18 there's a lot of other things going on during this
19 timeframe other than just FDA's actions. So, we'd have
20 to be very careful if those comparisons span a number of
21 years.

22 DR. RAPPAPORT: I would just add, if you're

1 trying to measure whether there's a reduction in abuse
2 in the community based on the change in formulation, I
3 don't see how that could be possible if a drug hasn't
4 been marketed out in the community.

5 DR. WOLFE: I agree fully with that, I'm just
6 simply saying the question a year ago was: Is some
7 reason to think that the new formulation is better? And
8 all I'm suggesting, that the community is essential, the
9 longitudinals are essential because people may get wise
10 to some of these tamper-resistant methods and
11 everything, but prior to approval, not in the community
12 in some kinds of studies, whether they're observational
13 studies or whatever, cross-sectional studies, randomized
14 trials between the two. Is it not possible to do more
15 of these studies before, some of them? Not as a
16 substitute.

17 DR. HERTZ: So, to do observational studies of
18 a non-approved product, what exactly do you mean?

19 DR. WOLFE: You literally could do a
20 randomized trial. I mean, prior to approval, you have
21 old OxyContin, it is around, still approved, you have
22 the new version, which has not yet been approved, but

1 it's obviously being subject to other kinds of studies
2 prior to approval. To get some better idea in addition
3 to the post-market studies what the evidence is that it
4 really has some improvement over the old product.

5 DR. HERTZ: So, you are envisioning a multi-
6 thousand patient study of new and old OxyContin, looking
7 for aberrant drug behavior?

8 DR. WOLFE: That would be one way of doing it.
9 There might be other ways of doing it. I'm just raising
10 the question. It just seems as we're struggling--

11 DR. HERTZ: I mean, I think that it's very
12 easy to throw out a concept.

13 DR. WOLFE: Right.

14 DR. HERTZ: Without having thought it through
15 because the concept of trying to look at abuse
16 aberrant drug-taking behaviors in a clinical trial of
17 patients is extremely difficult because they don't tell
18 you that their intent is to misuse or abuse. So,
19 typically, we get pretty low rates of this type of
20 behavior, particularly, I would imagine, if that's what
21 the intent of the study would be. So, I think we would
22 love to be able to come up with a design to look at this

1 pre-approval, but if you have actual thoughts on how it
2 can be done, that would be helpful, other than to say
3 something, because that's where we're here for.

4 DR. KIRSCH: Well, I think the question has
5 been asked and answered. We'll go on to the next
6 question.

7 Dr. Mendelson?

8 DR. MENDELSON: Yes, hi. Thank you. This
9 comes to about three different people who presented.
10 But the question for the Prescription Drug Monitoring
11 Programs, a big question would be: Do they capture data
12 from the mail-in pharmacies like Merck-Medco?
13 Increasing numbers of patients fill their prescriptions
14 in three-month intervals through long-term pharmacies,
15 and I think this may be fueling some of the supply of
16 licit opioids that become illicit. It would seem to me
17 important for epidemiologists to begin capturing who
18 pays for the medications and how many dose units are
19 dispensed at a time.

20 Dr. Lapteva, your wonderful slide there that's
21 the scariest slide I've seen as a practicing doctor,
22 says that most of the diverted opiates are coming from

1 single physicians prescribing to single patients. And
2 that sort of suggests that a large number of dose units
3 are going out to those individuals, and that is probably
4 occurring because of the way they're paid for. So, this
5 gets to Dr. Bickel's point that economics are important,
6 but they may not be the economics we think.

7 So, my question would be: How would we
8 capture payment sources for medications and how those
9 relate to the amount of abuse-able drug there is, and
10 this is something the FDA could possibly take a stand on
11 to say that there is going to be a limit on the number
12 of dose units dispensed in a per unit of time per
13 patient. This will not please the cost people because it
14 will drive costs up as people will need to be seen more
15 often for management. But it's an important point, I
16 think. It's not covered in any of the presentations so
17 far, it's who's paying for these drugs, for the most
18 part, and I think it's insurance is paying for all the
19 abused, and, therefore, we are all paying for them,
20 everyone who pays a premium for an insurance plan is
21 paying for medication. So, I'd like some comments from
22 the epidemiologists as to how would they capture who's

1 paying for the drugs and how would that be captured in
2 Prescription Data Monitoring Systems, as well, for out-
3 of-state prescriptions, which are probably not showing
4 up, at least on my prescription monitoring reports.

5 DR. STAFFA: Well, I can address that at the
6 population level, the drug utilization data that Dr.
7 Dormitzer talked about does capture mail-order
8 prescriptions, it captures all different sources,
9 whether it's retail, and so, that type of use is being
10 captured if we use that type of denominator. I'm not as
11 familiar with the Prescription Drug Monitoring Plans. I
12 don't know if someone else can address that.

13 MR. PAULOZZI: I can comment on that. Some
14 Prescription Data Monitoring Programs in states do
15 capture mail-order prescriptions to their state
16 residence. They don't necessarily capture them mailed
17 out of the state elsewhere. Others do not. So, it's
18 incomplete. I don't know what percentage of states fall
19 in each camp. I think that it's an important point that
20 it does need to be captured. The net effect of not
21 capturing it, of course, is to underestimate the total
22 number of prescriptions, the number of doctor shoppers

1 if people getting multiple prescriptions through that
2 route. Of course, there are limits in terms of how many
3 months' supply controlled substances can be prescribed,
4 but even single-month supplies could be ordered through
5 mail-order pharmacies.

6 If there's somebody from the DEA, they might
7 be able to comment more on that topic.

8 DR. KIRSCH: Dr. Omoigui?

9 DR. OMOIGUI: A couple of things. The first
10 question is to Dr. Paulozzi. There's a significant
11 difference in the percentage of injectable OxyContin
12 compared to injectable morphine. Is that a difference
13 because the injectable formulation of morphine is
14 commercially-available or has that been broken down into
15 what is being injected from commercial formulations and
16 what's being injected by kitchen chemists with respect
17 to the morphine? We know that OxyContin does not have
18 any commercially-injectable formulation. That's the
19 first question.

20 And the second thing I wanted to point--

21 DR. KIRSCH: Let's take one question at a
22 time, okay?

1 MR. PAULOZZI: Yes. Thank you. That data
2 that was not broken down by the formulation of the kinds
3 of drugs. So, I don't have really the answer to your
4 question. And it may be related to the injectable form
5 of morphine, but I don't know.

6 DR. KIRSCH: Okay. Your second question?

7 DR. OMOIGUI: The second question, there has
8 been some reference to a behavioral economics. As a
9 physician on the frontline, I can see that one of the
10 studies not being done here and which I believe would be
11 a leading indicator of the success of the new
12 reformulated OxyContin is what is the price point at
13 which OxyContin is being sold on the street?

14 Right now, one of the greatest problems we
15 have with OxyContin is 80 mg tablets, which is being
16 sold at \$1 per mg, you're getting like \$80 per pill, and
17 maybe with a little bit of discount, the person doing a
18 diversion gets \$50 a pill. Now, if you're talking about
19 prescription of 90 tablets, you're getting \$50 a pill
20 for a month's supply. You're essentially making after
21 tax income of \$100,000 a year.

22 So, I think if we're going to analyze the

1 success of this abuse-deterrent formulations, we also
2 need to know are the street prices dropping because that
3 would be an indicator of the desirability of this new
4 formulations. I don't know if anybody would be
5 interested in incorporating that into any of the
6 studies.

7 DR. KIRSCH: Would someone from the FDA like
8 to address that or should I call on somebody?

9 DR. RAPPAPORT: Let me just say, I mean, it's
10 an interesting concept, but I think really that's part
11 of the discussion that we're asking you all to have
12 tomorrow in response to the questions. What we're
13 looking for right now is that you get clarification from
14 the various speakers.

15 DR. KIRSCH: Thank you.

16 Dr. Flick?

17 DR. FLICK: Dr. Woodward, I just want to
18 better understand some of the datasets here. You talked
19 about in the TEDS dataset that most states do not
20 collect identifiers, which suggests that some states do
21 collect identifiers, and is there an opportunity in
22 those states to do longitudinal studies?

1 DR. WOODWARD: We've looked into that. It's
2 difficult because the data isn't really that well
3 collected. We also face restrictions on doing that kind
4 of analysis, the confidentiality privacy issues that I
5 alluded to. The states have their own regulations. I'm
6 not really in that group, so, I can't really respond as
7 fully as I might want to or you might need, but I know
8 the others in that group have looked into it, and it's
9 been difficult logistically to get those kinds of
10 studies going on. We haven't been sure that the data
11 quality is that good that it would be that useful. I
12 know certain states do have good data. They've done
13 their own analysis, done their own reporting on that.

14 DR. FLICK: I would think that the ability to
15 collect identifiers and the ability to do longitudinal
16 studies is crucial to having good data with regard to
17 this question, and I would think or I would hope that we
18 could answer that question clearly. So, if there is an
19 opportunity to do those studies and select the states,
20 that we avail ourselves of that.

21 I also wanted to ask with regard to DAWN, this
22 is a probability sample of short-stay federal hospitals.

1 Does that include rural hospitals? Is there a bed size
2 cutoff for that? Are we eliminating rural hospitals
3 where I think a good proportion of this problem exists?
4 And do we include children's hospitals in that dataset?

5 DR. WOODWARD: We include rural hospitals.
6 Obviously, they're not going to show up as part of the
7 metro area over-sampling; they're going to be part of
8 the remainder sample. We can do some reporting on rural
9 versus non-rural, but EDs, the sample is strong enough
10 for that. We would only include children's hospitals if
11 they have an emergency department that's open 24 hours,
12 7 days a week. But, generally, I mean, we only use
13 short-term general hospitals, so, I can't think of any
14 in the 200, 250 hospitals that would be children's
15 specialty hospitals.

16 DR. FLICK: All right. I would think that is
17 going to be a problem from an epidemiologic standpoint
18 if the age that we're considering here is 12 and over,
19 especially in metropolitan areas, where a lot of the
20 pediatric emergency care takes place in a children's
21 hospital. You will miss all of those or many of those
22 patients.

1 DR. WOODWARD: Well, the DAWN does pick up
2 under 12; it picks up all age groups. It's the NSDUH
3 that's 12 and over.

4 DR. FLICK: If it doesn't sample, then they
5 won't be represented or they won't be accurately
6 represented. If you're not sampling children's
7 hospitals, then you're sampling metropolitan areas.
8 They'll be missed.

9 DR. WOODWARD: No, it's a limitation. I
10 agree. It's also expensive to add to--I mean, we'd also
11 like to sample especially psychiatric facilities, too,
12 which that would be more consistent with SAMHSA's
13 missions.

14 DR. FLICK: I certainly understand the
15 limitations.

16 DR. WOODWARD: Yes.

17 DR. FLICK: And I'm not being accusatory here.

18 DR. WOODWARD: Yes.

19 DR. FLICK: I'm just saying if we're going to
20 plan studies, we need to understand what the datasets
21 contain and what they more importantly don't contain.

22 If I could just ask one more question of you.

1 DR. WOODWARD: Sure

2 DR. FLICK: Do any of these datasets
3 communicate with one another or can the data from one be
4 merged with another to gain a more accurate picture?

5 DR. WOODWARD: Could I, if it's okay,
6 elaborate a little more on your prior question?

7 DR. FLICK: Sure.

8 DR. WOODWARD: One of the things that we have
9 been looking into, the staff has been looking into is
10 working with other ED databases. NCHS has the NHAMCS
11 and also ARHQ has the SIDS and SAIDS part of the HCUP,
12 the Hospital Cost Utilization Project. Again, they're
13 largely focused on general hospitals, but they do get
14 into specialty hospitals more than we do. So, we're
15 trying to supplement.

16 DR. FLICK: Right. The Age CUP database
17 contains an additional sub-database called the KID
18 dataset, which, if I'm not mistaken, has identifiers and
19 can accurately represent pediatric care. So, it might
20 be an opportunity to utilize that dataset to better form
21 a picture of pediatric care.

22 DR. WOODWARD: Yes, we're starting to talk

1 with AHRQ, and we've started to talk to NCHS.

2 DR. KIRSCH: We're going to go to the next
3 presentation.

4 DR. WOODWARD: Okay.

5 DR. KIRSCH: For a point of clarification, Dr.
6 Morrato is shaking her head no, and so, I'll give one
7 second.

8 DR. MORRATO: Yes, I've done research with
9 KID. KID is admissions, it's the identified. If you're
10 really interested in pediatric, there's a semi-
11 proprietary PHIS dataset which would allow you to get to
12 that.

13 DR. KIRSCH: So, our next speaker is Dr.
14 Kornegay.

15 **Study Designs to Assess Prescription Drug Use**
16 **Design Considerations in Epidemiological Studies of**
17 **Abuse-Deterrent Opioids**

18 DR. KORNEGAY: Good morning. My name is
19 Cynthia Kornegay, and I'm an epidemiologist in the
20 Office of Surveillance and Epidemiology at FDA. I'm
21 going to spend the next several minutes discussing some
22 general design considerations related to epidemiological

1 studies of opioid abuse.

2 First, I will outline the purpose of this
3 talk. I am also going to briefly review the definitions
4 of abuse and misuse. Then I will provide some
5 background information, and, finally, discuss
6 comparators and issues related to measuring change in
7 abuse-related outcomes in studies. I will conclude by
8 summarizing the concerns highlighted in my presentation.

9 The purpose of this presentation is to provide
10 general comments based on preliminary proposals
11 submitted by the Sponsors and to provide a framework for
12 considering the industry presentations later this
13 afternoon and tomorrow. My talk will relate mostly to
14 study design, while the next talk will address some of
15 the statistical considerations. This presentation is
16 not a detailed critique of the specific proposals, but
17 general comments based on the submitted documents.

18 To review, abuse is defined as the non-medical
19 use of a drug repeatedly or sporadically for the
20 positive psychoactive effects it produces, while misuse
21 is defined as the use of a drug outside label
22 directions or in a way other than prescribed or directed

1 by a healthcare practitioner. The difference is intent.
2 For abuse, the intent is non-therapeutic, that is to get
3 high, while the intent is still therapeutic for misuse.
4 These definitions are independent of anything that may
5 be done to the drug, for example, crushing, dissolving,
6 chewing, et cetera, to achieve the desired effect.

7 The proposals that you will hear about will
8 use differing approaches, measuring a particular
9 population versus studying several different populations
10 and measuring the severe end of the abuse spectrum
11 versus including occasional or recreational use. Both
12 proposals attempt to measure change, but that raised the
13 question of change from what?

14 Prior to measuring change, the baseline abuse
15 potential for a product would need to be established.
16 This would also be important in targeting studies and
17 interventions to where they will have the largest
18 impact. One of the basic considerations is defining who
19 is at greater risk for abusing a particular product,
20 including demographic, social, economic, and geographic
21 considerations in defining at-risk populations may help
22 define the limits of abuse deterrence efforts. In

1 addition, other risk factors such as family history and
2 certain psychological conditions may also be important
3 in determining the at-risk population.

4 Along with who at-risk individuals are, how
5 they are manipulating the product or not is also
6 important. In other words, are a product's abuse-
7 deterrent properties designed to affect the typical
8 routes of abuse? Before a change in abuse-related
9 outcomes can be measured, the baseline abuse level
10 population and risk factors must be known. This
11 information can be determined from historical data on
12 the same or similar products. This baseline should be
13 derived from real world, that is post-approval, product
14 use.

15 The next few slides will discuss the important
16 issue of comparators. The appropriate comparator is
17 vital to providing the big picture or context for
18 changes in abuse-related outcomes. There are several
19 different choices for meaningful comparators, but,
20 usually, multiple comparators are required. Multiple
21 comparisons can be historic by class, drug schedule,
22 and/or individual product. Specific attributes of

1 comparators will be discussed in more detail shortly.
2 Although multiple comparisons on many levels are
3 necessary to understand the big picture. They can be
4 confusing, and conversely make it more difficult to
5 understand what is going on.

6 In some cases, it will be possible to compare
7 non-abuse-deterrent and abuse-deterrent formulations of
8 the same product from either a historic or concurrent
9 perspective. This could be a particular problem,
10 however, for novel drugs introduced with abuse-deterrent
11 formulations. Once an abuse baseline is established,
12 how will it be possible to determine if abuse-deterrent
13 properties are effective?

14 Although these challenges are familiar, when
15 deciding on what comparators to use, this is a partial
16 list of some of the attributes that should be
17 considered. Ideally, comparators should be similar in
18 population, indication, active ingredient, time-released
19 formulation, single ingredient or combination, and time
20 on market. One should also consider the strength, route
21 of administration, and the scheduling. The next section
22 will provide some thoughts on interpreting a change in

1 abuse.

2 Although none of these questions have easy
3 answers, some are more abstract and may require a
4 paradigm shift to address effectively. The most obvious
5 question is what is a significant change and how can
6 that be defined? Close on heels of that is what types
7 of change are most meaningful from a regulatory
8 perspective, a change in the common methods of abuse or
9 an overall reduction as an example? Other questions are
10 over what time period should the change occur and in
11 what population?

12 A second consideration in measuring change is
13 how time will be incorporated. It would be unrealistic
14 to assume that the abuse profile of a drug would be
15 static once established. The abusing population and the
16 method of abuse are both subject to change.

17 To address this, should updates be triggered
18 at some pre-defined point or be scheduled on a product-
19 by-product basis? In addition, how comprehensive should
20 updates be? That is, what level of detail is necessary
21 to detect a shift in the baseline assessment or in abuse
22 levels?

1 A third issue is a population that is studied.
2 How should high-risk populations be weighted in a
3 baseline abuse assessment? Should traditional high-risk
4 populations always be included, and what about the
5 general population? Addressing these concerns will
6 require careful consideration of when data are available
7 relative to when they are collected and of unrelated
8 events that may affect baseline abuse levels. It may
9 also require the ability to modify or augment currently
10 existing data resources.

11 In addition to prior population
12 considerations, it is not clear how results from
13 numerator-only sources should be weighed in the national
14 context. Also, what is the value of small, focused,
15 non-epidemiologic studies? How can they contribute to
16 improving or refining the abuse profile and safety
17 issues of a particular product?

18 In an effort to increase the quality and scope
19 of data available to assess abuse-related outcomes.
20 Several non-traditional data resources are under
21 consideration. These include health care systems such
22 as Kaiser, convenient samples or surveys, and add-ons to

1 population-based surveys and questionnaires. While
2 these data sources can provide detailed information,
3 data resource validation, as well as sample size and
4 power considerations will still need to be identified
5 and appropriately addressed. It will also be necessary
6 to determine the relative importance of study results.
7 Should they be limited to reporting findings from more
8 commonly-used data resources or are they robust enough
9 to be viewed as an independent study?

10 A final consideration is somewhat less
11 concrete, but still carries important implications for
12 determining the impact of abuse-deterrence measures.
13 Most studies implicitly assume that less hardcore users
14 means less casual users, but it is not always clear that
15 that is a simple relationship, and, from a public health
16 perspective, is a most effective abuse reduction
17 strategy when the target's new initiates, hardcore
18 users, or individuals who are transitioning from one
19 extreme to the other?

20 To summarize, this presentation presented
21 several ideas to keep in mind while listening to the
22 upcoming presentations. Has a good baseline picture of

1 the at-risk population mechanism been established prior
2 to measuring the effect of abuse-deterrent mechanisms?
3 Are the abuse-deterrent mechanisms designed to address
4 major or problematic routes or methods of abuse?

5 If multiple studies are proposed, will they be
6 completed in sequence or concurrently? How much
7 influence should numerator or sub-national studies have
8 on the overall abuse profile? Have the appropriate
9 comparators been selected? Have timing issues, the time
10 to create a baseline abuse profile, the time to
11 determine appropriate study length, and decide to
12 include time-dependent outcomes been considered and
13 incorporated into the study design? If novel data
14 resources or collection methods are proposed, how will
15 they be validated?

16 And finally, there were several population-
17 related questions. Is the proposed population similar
18 to the at-risk population? Have demographic, co-morbid,
19 and geographic issues been appropriately incorporated?
20 Should the study target high-risk individuals? Should
21 hardcore users, recreational users, or both be included?
22 Also, what are the implications of performing the study

1 in a non-traditional data resource?

2 Thank you.

3 DR. KIRSCH: Thank you. The next speaker is
4 Dr. Keeton.

5 **Statistical Considerations for Epidemiological Studies**
6 **of Abuse-Deterrent Formulations**

7 MS. KEETON: Good morning. My name is
8 Stephine Keeton, and I am a statistical safety reviewer
9 in the Office of Biostatistics at FDA. Today, I will
10 present the statistical considerations for
11 epidemiological studies of abuse-deterrent formulations
12 of opioids.

13 The purpose of this talk is to highlight and
14 discuss general statistical issues based on the
15 preliminary study proposals submitted by the Sponsors.
16 I will not provide a detailed critique of the
17 proposed statistical analyses, but, instead, will raise
18 general issues for consideration. This talk is in
19 conjunction with Drs. Dormitzer and Kornegay's talks
20 that you've just heard.

21 Here is an outline of the presentation. I
22 will start by briefly discussing the trend and Cross-

1 Sectional Approaches described in the proposals. I will
2 then discuss some general modeling issues, followed by
3 issues related to data sources. I will also discuss
4 sample size and power considerations. And finally, I
5 will discuss multiplicity and replication issues before
6 summarizing the statistical considerations.

7 The overall goal of the Epidemiological
8 Program proposals is to show a reduction in the rates of
9 death, overdose, or abuse by comparing drug products and
10 formulations. One method to compare the rates is the
11 Trend Approach. This is the primary approach used in
12 the OxyContin Program. The Trend Approach compares
13 rates before and after the introduction of a new
14 formulation. This approach can also be used to compare
15 rates across time after introduction of a new
16 formulation.

17 The graphic on the left-hand side illustrates
18 the approach of comparing rates before and after
19 introduction of a new formulation. The X-axis
20 represents time and the Y-axis represents the rate of
21 the outcome. For a product that has been on the market
22 for a considerable time such as OxyContin, the trend

1 approach compares the rates before and after
2 introduction of the new formulation. The red dash line
3 represents the time of introduction of the new
4 formulation. Two effects on the rate are considered.
5 First, a change in the mean level of the rates before
6 and after introduction of the new formulation, and
7 second, a change in the slope of the rates before and
8 after introduction. It is important to observe what
9 happens to rates for some period of time before and
10 after introduction of a new formulation.

11 The graphic on the right side illustrates the
12 Trend Approach for other opioid products. Changes in
13 the rates within a population over time may be
14 occurring. These changes may be influenced by other
15 factors such as the introduction of risk, evaluation,
16 and mitigation strategies or changes in cultural
17 behavior related to abuse. These changes in rates from
18 such factors should be accounted for in the analysis.

19 Another approach proposed is the Cross-
20 Sectional Approach. This is the primary approach used
21 in the Embeda Program. The Cross-Sectional Approach
22 compares rates for a new formulation to other products

1 at a specific point in time or over a short period of
2 time. The graphics on this page illustrate the Cross-
3 Sectional Approach.

4 Again, the X-axis represents time, and the Y-
5 axis represents the rates of the outcome. Time 1 on the
6 X-axis denotes some period of time in which a comparison
7 between drug A and other drugs is made. The comparison
8 can also be made at an additional time point, time 2 to
9 evaluate whether the effect remains constant.

10 In this slide, I will talk about some
11 considerations of the trend and Cross-Sectional
12 Approaches. The Trend Approach offers intuitive
13 graphics and analytic summaries. In this approach, it
14 is important to control for changes over time and
15 secular factors related to the outcome of interest. The
16 Trend Approach can also be used to compare rates across
17 time after introduction of a product.

18 For example, for Embeda, the Trend Approach
19 could be used to look at the effect of the drug over
20 time after introduction of the new formulation. In
21 absence of randomized treatment assignment, other
22 factors may confound association between the product and

1 the rates. The Cross-Sectional Approach provides a
2 snapshot of abuse in time. However, the effect over
3 time may not be constant and must be considered. Again,
4 in the absence of random treatment assignment, other
5 factors may confound association between a product and
6 the rates.

7 In the next couple of slides, I will discuss
8 some issues related to modeling of outcomes, death,
9 overdose, and abuse. The analysis should control for
10 potential confounders such as possible patient selection
11 biases. Physicians may preferentially prescribe an
12 abuse-deterrent formulation to patients suspected to
13 abuse opioids, and this may result in higher rates of
14 abuse. Additionally, patient characteristics may differ
15 across time. Techniques such as multivariate analysis
16 and propensity score methods may be used to adjust for
17 differences in patient characteristics across
18 formulations and time.

19 When considering the model for these studies,
20 it is important to note whether drug availability is
21 included in the model as a covariate or not. For
22 example, in one of the Embeda studies, several models

1 are proposed to compare rates. The primary model does
2 not adjust for drug availability. Without adjusting for
3 drug availability, the model provides estimates of the
4 proportion of abuse by unlabeled routes of
5 administration among all users. The secondary model
6 does address for drug availability. The model provides
7 rates of abuse by any route of administration among all
8 users. The difference in interpretation of the models
9 should be considered when selecting a model.

10 I will now discuss some issues related to data
11 sources. The data source should represent the
12 population of interest, for example, abusers versus all
13 users, and enriched population, such as abusers from
14 substance abuse treatment centers, may be easier to
15 study since it will provide more events of interest. I
16 will discuss this topic more later when I discuss power
17 in sample size issues.

18 Some of the studies propose, such as studies
19 conducted from data using data from substance abuse
20 treatment centers and special populations are based on
21 convenient samples. Caution must be taken when
22 interpreting results from these studies since

1 generalizing the results to a population that has
2 clinical relevance may be difficult. When interpreting
3 these studies, the results of such studies, one should
4 characterize how the study subjects differ from the
5 population of interest, in particular, pay attention to
6 who might be left out or underrepresented in the data.

7 The appropriateness and accuracy of
8 denominator information should also be considered to
9 ensure meaningful interpretation of the data.
10 Statistical surveys provide denominator estimates.
11 Well-designed and conducted surveys provide valid
12 denominators. Administrative claims data provide
13 internal denominators. However, these databases may not
14 represent the population of interest. For studies that
15 provide only numerator information, for example, poison
16 control data, the denominator must come from other
17 sources. For such studies, the appropriateness and
18 accuracy of the denominator source should be considered.

19 Power and sample size determination are
20 necessary if the study is to be used for statistical
21 inference. The sample size impacts the feasibility of
22 conducting the study. The statistical power and sample

1 size depend on the event rate which I will discuss in
2 more detail in the next slide. As well as the effect
3 size and length of time period for trend analyses. As
4 stated in Dr. Kornegay's talk, defining a significant
5 reduction is a critical component of designing studies
6 to measure change. The required effect size is based on
7 clinical relevance. The smaller the effect size one
8 wants to detect, the larger the sample size required.
9 For trend analysis, the length and number of time
10 periods must be taken into consideration. The longer
11 the time period, the more information, and, therefore,
12 more likely it is to precisely identify patterns of
13 change.

14 Statistical power depends highly on the number
15 of events captured in a study. More events provide
16 greater statistical power. Studies of enriched
17 population such as studies of patients entering
18 substance abuse treatment centers will likely offer a
19 relatively high number of events, and, thus, easier to
20 study. The choice of outcome also impacts power, as
21 more frequent outcomes are easier to study.

22 The duration of the study also impacts power

1 in that the longer the duration, the more events
2 observed. The event rate of the comparator drug or
3 comparative period needs to be considered. Again, more
4 events provide greater statistical power.

5 Finally, product availability impacts a number
6 of events. If a product is not readily available to
7 use, it may take a considerable amount of time to get
8 events. If any assumptions used to calculate the sample
9 size are incorrect, the study may be underpowered and
10 not capable of demonstrating an effect.

11 The various studies proposed addressed
12 different populations and questions, but may provide
13 overall information on abuse. However, other sources of
14 data may be required to replicate the results. Testing
15 abuse deterrence over time raises statistical issues.
16 As stated in Dr. Kornegay's talk, the abuse profile of
17 the new formulation may change after some period of time
18 of being on the market. This may require multiple uses
19 of the same data sources and adjustments for multiple
20 testing may be required.

21 In summary, the Sponsors have proposed two
22 general approaches to measure the abuse-deterrent effect

1 of new formations. For both the Trend and Cross-
2 Sectional Approaches, there are several important
3 statistical issues to consider when reviewing the abuse-
4 deterrent studies. The analysis should control for
5 potential confounders, such as possible patient
6 selection biases and consider methods to adjust for
7 differences in patient characteristics across
8 formulations and time. The relevance of the data source
9 to the population of interest should be considered, as
10 some studies will be conducted using data based on
11 enriched populations or convenient samples. The
12 appropriateness and accuracy of Denominator information
13 may have an impact on study quality.

14 The statistical power and sample size depend
15 on the choice of outcome population, duration, and drug
16 availability. These factors does affect the study
17 feasibility.

18 And lastly, the abuse profile of the new
19 formulation may change after some period of time of
20 being on the market. Multiple uses of the same data
21 over time should be accounted for in the statistical
22 inference.

1 Thank you for your attention.

2 DR. KIRSCH: Thank you. Before we break for
3 lunch, I want to ask for any of the morning speakers
4 whether anybody who spoke this morning is not going to
5 be here this afternoon. My preference is to hold the
6 further questions to this afternoon, but if any of the
7 speakers from this morning plans to leave at the
8 lunchtime and not come back, I'd like to direct any
9 questions. There's one. So, we have one speaker who's
10 not coming back, and that's the person from the DAWN
11 Group. So, are there any questions any member of the
12 committee has for that individual speaker before we
13 break for lunch?

14 Seeing no hands, I'll assume that there will
15 be no questions for that individual, and we will break
16 for lunch now. It's currently 11:55. I will now break
17 for lunch. We will reconvene again in one hour in this
18 room at 12:55. Please take your belongings you may want
19 with you at that time.

20 Committee members, please remember that there
21 should be no discussion of the meeting during lunch
22 amongst yourselves, with the press, or any member of the

1 audience. Thank you.

2 (Whereupon, at 11: a.m., a luncheon recess
3 was taken.)
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21

22 A F T E R N O O N S E S S I O N

PRECISE REPORTING, LLC

(12:55 PM)

DR. KIRSCH: I'd like everybody to take their seats. We're going to reconvene the meeting.

The first session of this afternoon is to address additional clarifying questions. I want to remind the members of the committee that really the purpose that we're here for for these two days is really to help FDA come up with relevant studies to encourage the companies to use in order to look at the outcomes that we think are important. It's really not to necessarily criticize one company or another; it's to really help the FDA come up with studies, which I find it to be a very exciting opportunity.

So, in that context, we're going to go back to our question list, which is--I think, actually, I cut off Dr. Flick when he was talking before. I want to make sure he asked all of his questions.

Clarifying Questions

DR. FLICK: I did have one other question, and the question that wasn't answered was: Do we have the capacity to merge information from one dataset to another? And I don't know which one of the presenters

1 can address that question. Which of any of the datasets
2 can merge their data to make a more robust dataset?

3 MR. PAULOZZI: I guess I can try a partial
4 answer to the question. You need, of course, personal
5 identifiers. So, that would mean medical examiner,
6 coroner information, or vital statistics information for
7 deaths, and that information has been, can be merged
8 with--

9 DR. FLICK: No, I think we're maybe talking
10 about two different things. For example, as I've used
11 before, the National Hospital Discharge Survey, for
12 example, uses the same methodology as the National
13 Survey of Ambulatory Surgery. So, the methodology and
14 the sampling universe can be merged to make an accurate
15 representation of surgical procedures in the U.S., for
16 example. So, I think those are a little bit different
17 things that we're--

18 MR. PAULOZZI: Yes, yes, and I don't have an
19 answer to that question.

20 DR. FLICK: Okay.

21 DR. KIRSCH: Okay, and then Dr. Morrato had a
22 question that she was going to ask during the break and

1 I cut her off because it wasn't in the public forum, so,
2 I asked her to ask her question in the public forum.

3 DR. MORRATO: Okay. It was a question related
4 to CDC, and maybe a little bit of what we've discussed
5 before in terms of what can be done before a drug is
6 approved. I know in other areas of public health,
7 they've taken approach of system dynamics modeling.
8 They've used this, for instance, to model national
9 cocaine prevalence, and, most recently, there was a
10 special issue July of the *American Journal on Public*
11 *Health*, where they were talking about this is a way of
12 looking at tobacco control.

13 And, so, my question was whether or not anyone
14 has done sort of this theoretical framework that looks
15 at sort of the abuse of prescription opioids as a
16 starting point. So, as we're looking at these different
17 interventions, you might be able to predict which might
18 work better than others.

19 So, for instance, so, it's a system dynamics
20 modeling, it allows you to model multiple interactions
21 of diseases, risk, delivery systems, populations that
22 we've been talking about, and how it relates to national

1 and state policy. So, it's more of a modeling exercise,
2 but then it gives guidance for what might be
3 interventions and/or measurements, et cetera. And I
4 don't know the field well enough whether or not CDC
5 folks are aware of it or anyone.

6 MR. PAULOZZI: I'm sorry; I'm not familiar
7 with that modeling approach. I would think though it
8 depended on the availability of multiple variables about
9 individuals involved, and it seems like the constant
10 problem in this is that you don't have a lot of in-depth
11 information about individuals using the drugs.

12 DR. MORRATO: Yes, so, it's more of a
13 conceptual framework where it's social sciences create
14 the model, and then you put information in it as you
15 acquire it, but at least you're starting with a
16 framework.

17 MR. PAULOZZI: Yes.

18 DR. ANTHONY: The RAND Group probably launched
19 the best starting points for those systems analysis
20 models having to do with cocaine and other drugs. The
21 best work that's been done since then is probably
22 Jonathan Caulkins' work. He works with a group in

1 Vienna, as well. Jonathan is a Carnegie Mellon.

2 And then the elaboration with some more
3 sophisticated statistical models is being done by
4 Georgiy Bobashev at Research Triangle Institute. So,
5 there are developments, but it's pretty cartoon-like.
6 You can make some predictions. Validating the
7 assumptions is difficult, but I think it's a very good
8 suggestion and a line to work. They've done some pretty
9 good work on that.

10 DR. KIRSCH: Okay. Dr. Bickel?

11 DR. BICKEL: I have two questions. I'll ask
12 them one at a time. And this one is for everybody who
13 has different datasets. So, given that addiction has a
14 strong monotonic association with social economic status
15 that is whether you measure it by educational attainment
16 income or occupational status. The lower your
17 education, the lower of your income, your lower
18 occupational status, the more likely you are to use
19 drugs and to be addicted. Has anyone used these
20 different datasets to model the fact that that is the
21 case and use that to make inferences about who is
22 susceptible?

1 DR. ANTHONY: I'm sorry. I have to start by
2 challenging your assumption. It depends really heavily
3 on stage of introduction of the drug and the population,
4 and earlier in the stages, there's often an excess among
5 high SES individuals, and in later stages, things
6 straighten out. Tobacco smoking epidemic is an
7 excellent example of that in the United States right
8 now. cocaine, there's someone sitting in this room
9 who's published on this topic in relation to cocaine
10 using the National Surveys on Drug Use and Health and
11 the national household surveys. So, yes, work has been
12 done, but I don't think I'd have as a starting point the
13 assumption that you started with. Okay.

14 DR. BICKEL: Fair enough. My second point,
15 and, Jim, you started to address this, right? So, who
16 are the early adopters, and should we have a model of
17 them and see whether they're predictive of later use
18 patterns so that we could actually use them as like a
19 canary in the coal mine?

20 DR. ANTHONY: In my slide on future
21 directions, I planted a little seed, and I'm happy that
22 you've given me a chance to see if it can blossom. If

1 the regulations allow limited release to subpopulations,
2 there would be some groups that would be useful to try a
3 limited release form of experiment, and those would be
4 hospitals where you know quite a bit of opioid diversion
5 is going on with existing established products. And
6 under fairly carefully controlled conditions, you could
7 release the new product and see what happens in a
8 population where you know there are hospital personnel
9 who will figure out ways to divert new products.

10 So, I think I'd encourage FDA to think about
11 this as a way of staging the introduction of the product
12 in different subpopulations that might vary in their
13 vulnerability. A long time ago, and this is probably
14 when Dr. Wolfe and I didn't have any gray hair, I
15 recommended FDA randomly assigning regulatory regimes to
16 different states when new products were introduced. I'm
17 pretty sure the Boards of Pharmacy and the like would be
18 open to this, particularly if it would lead us to better
19 evidence about the effect of different regulations and
20 the impact of different compounds.

21 DR. KIRSCH: Dr. Denisco?

22 MR. DENISCO: Thank you. A couple of comments

1 along with a question to possibly Dr. Paulozzi and
2 anybody else.

3 One is we looked at populations. We briefly
4 discussed subpopulations that we needed to pay attention
5 to in pediatric populations were mentioned. Another
6 population that I think needs to be mentioned is the
7 prisoner population. We have almost 1 percent of the
8 population is incarcerated, and especially with the
9 NSDUH study, that doesn't sound like 1 percent would
10 affect the statistics very much, but a little back of
11 the napkin calculation, when you look at the high
12 prevalence rate of addiction in that population, it can
13 really throw things. So, I was wondering if there was
14 any way better than the back of the napkin to sort of
15 address that. That was one thing.

16 The second thing is --

17 DR. KIRSCH: Well, let's hold off for the
18 first question first. Was the question pointed at Dr.
19 Paulozzi?

20 MR. PAULOZZI: So, you're asking whether or
21 not the surveys can be affected by not including
22 incarcerated populations and how that can be affected?

1 Yes, I can see your point, 1 percent with a
2 tenfold great prevalence of addiction might really make
3 a difference in the statistics. I don't have an answer
4 though in terms of how to address that particular
5 problem since that would be an issue really for the
6 SAMHSA people to try to address how to involve that
7 population. They do have surveys of drug use of
8 perpetrators who were arrested, ADAMS System, which gets
9 at drug use and screens people at intake after arrest,
10 which gives you some sense of drug prevalence or use of
11 drugs in that population.

12 DR. KIRSCH: Dr. Anthony?

13 DR. ANTHONY: So, if you live long enough, you
14 get to make many sins. We actually did what you're
15 proposing that we should do. In the NIMH Epidemiologic
16 Catchment Area studies in the early 1980s where we had
17 coordinated samples of household, institutional, and
18 homeless individuals, and institutions included prisons
19 and jails and nursing homes and the like, mental
20 institutions. We really didn't find much variation in
21 the estimates, although, of course, there are
22 concentrations of the cases where you would predict.

1 But it turns out the relative proportions in those
2 subpopulations are small enough that they don't really
3 perturb the estimates when you take the confidence
4 intervals of the estimates into account. Because any
5 single point estimate is not going to be all that
6 helpful, but if you put a confidence interval around it
7 and then ask how often are you moving the estimate
8 around outside of the confidence interval, it didn't
9 really happen very much.

10 Subsequently, I don't believe any of the
11 investments, and we're talking about more than \$1
12 billion in the early 1980s in these surveys. I don't
13 think any of the subsequent studies have included
14 coordinated household, non-household populations as we
15 did there. Perhaps because we didn't find that it made
16 all that much difference, but, as Len pointed out, there
17 are special studies of prisoners and special studies of
18 the homeless and so on.

19 DR. KIRSCH: Okay. Go to your second
20 question.

21 MR. DENISCO: Yes, the second question is:
22 Since the prescription drug problem is closely

1 intertwined with the pain medicine treatment and under
2 treatment of pain. Certainly, there's going to be
3 unintended consequences, and I would do an almost
4 proposed. It's not really a question, more a comment,
5 that any time these issues of prescription drugs are
6 studied, there should be some attention paid to what it
7 does to the availability of legal prescriptions to
8 appropriately screen patients.

9 DR. KIRSCH: I would bet that our open public
10 hearing tomorrow, we'll hear a lot about that.

11 Dr. Bilker?

12 DR. BILKER: Yes, I was wondering whether it
13 would be important and if any of the databases are
14 capable of assessing abuse by new or previously naïve
15 abusers of illicit drug versus continuing abuses. If
16 possible, that would allow estimation of barriers to
17 abuse as a deterrent to initiation of new abusers versus
18 continuing users.

19 I had one more question after that.

20 DR. KIRSCH: Dr. Anthony, did you want to--

21 DR. ANTHONY: You'll be happy to know it's
22 been done. So, within the limits of the assessment, you

1 can restrict your estimates to people who have used no
2 other drug before the one of interest and people who've
3 started with tobacco or alcohol and people who have used
4 cocaine and so on. So, that routinely is being done,
5 and the context of new products is a new one, and it
6 hasn't been done there because usually these surveys are
7 contracted out in five-year increments. The assessment
8 plans are laid out fairly well in advance, and the
9 capacity of the survey team to move quickly when a new
10 product is introduced is slow. I mean, it's there, but
11 it's slow and expensive.

12 Now, if you had asked me is it worth it to
13 make the expense of putting a piggyback assessment on a
14 standardized assessment in order to learn something of
15 value for the public's health, I'd say in many cases
16 we're going to find that it's worth the cost. But that
17 hasn't been done yet. Not to my knowledge.

18 DR. BILKER: Are any of the databases that
19 we're talking about capable of doing this? Making this
20 assessment?

21 DR. ANTHONY: In the existing data, you have a
22 trace for each individual of the age of onset of each

1 drug, and you also, for people who've used and started
2 to use in the past 24 months or so, you have month of
3 first use. So, you can actually get some pretty fine-
4 grained, temporal sequences for each individual, and
5 that would allow you to study these variations that
6 you're pointing toward.

7 DR. BILKER: Okay. Great.

8 DR. KIRSCH: Did you have a second question?

9 DR. BILKER: Yes. Just one point I wanted to
10 make about the Trend Approach, in looking at the trends
11 over time. It might be very important early on after
12 introduction of the drug to consider nonlinear effects.
13 You're looking at linear effects, but there might be
14 bumps as people figure out how to get the drug out.
15 You'll see bumps in the road. So, it'll be important
16 not to just look at linear effects.

17 DR. KIRSCH: Thank you.

18 Dr. Wolfe?

19 DR. WOLFE: This is for my gray-haired
20 colleague, Dr. Anthony, which was I'd just like to hear
21 a little bit more about your interesting concept of
22 processed phenotypes both in terms of how that could be

1 incorporated into post-approval surveillance or even
2 arguably into pre-approval looks. I mean, we obviously
3 are using amongst others as subjects for studies people
4 who are beyond that, who are clearly addicted or at the
5 other end of the spectrum who are new, but here's the
6 halfway, and it would seem that this is a sensitive
7 group to be able to assess whether or not X is going to
8 more rapidly move them towards the other end of the
9 spectrum.

10 Could you just comment on that, please?

11 DR. ANTHONY: Thanks for the opportunity. So,
12 let's think about the patient who's given one of the
13 opioids that has a relatively high side effect profile
14 for a dysphoric response. So, for pharmacokinetic
15 reasons or other reasons is generating dysphoria.

16 In that patient for that product, you wouldn't
17 expect more than one pill or so to disappear from the
18 dispensed container. And by doing a pill count study,
19 you might find a population that's very low susceptible
20 to the repeated use of the drug that would lead to a
21 dependent syndrome or subsequent problems. And then
22 you've got people who are given prescriptions say for

1 dental surgery, maybe a run for 14 days or something,
2 but after 2 days, the pain has subsided and the rest of
3 the product sits in the medicine cabinet. Those, again,
4 are going to be individuals who you'd suspect to be less
5 likely to develop dependence.

6 Now, what that leads me to then is to suggest
7 that very early monitoring of the dispensed
8 prescriptions to do pill count studies and to see how
9 often people are ramping them up, whether they ramp them
10 up more quickly for an established product versus a new
11 product, that's the kind of thing that I don't think has
12 been done, but could be done. Now, maybe we'll learn
13 from industry that it has been done, but I haven't seen
14 the published studies. But those are the very early
15 steps that you'd think that are leading toward this
16 outcome of dependence that would give us some early
17 clues about what might happen next.

18 And then time from the first use of the drug
19 to the second use of the drug is not routinely assessed
20 in any of these studies, but it would seem to me that
21 that interval is a very informative interval with
22 respect to the likelihood that someone's going to become

1 a repetitive user.

2 DR. WOLFE: Thank you.

3 DR. KIRSCH: Okay. We don't have any more
4 people who want to ask questions, so, we're going to go
5 on to the presentation by the Sponsor.

6 MS. BHATT: Dr. Walsh. I'm sorry.

7 DR. KIRSCH: I'm sorry. Dr. Walsh?

8 DR. WALSH: Thank you. Yes, actually my
9 question in part, I have two questions, but it falls on
10 from what Dr. Wolfe was just asking about. It seems
11 like we're being asked to be creative in thinking about
12 what needs to be captured in advance, but we're asking a
13 question that hasn't been answered before: How do we
14 detect a signal that's a change either historically or
15 to some kind of comparator? And my questions are
16 directed to Dr. Anthony. I was intrigued by your
17 creativity, and in the processed phenotype, thinking
18 about intent.

19 You said that you were asking about what have
20 you done and then what do you intend to do? And we have
21 heard from people about changes over time that may take
22 place, where people either determine that they can

1 compensate for the deterrent properties and you would
2 see an increase in use or alternatively, they may decide
3 that it really isn't worth the time and effort, and then
4 it really does have abuse-deterrent properties because
5 it's not popular among the abusers. And I'm wondering,
6 trying to get at the questions of why, what can we learn
7 about the motives between first and second use and
8 strategies for misuse, what can we incorporate into
9 these kinds of studies to ask the questions about why
10 and actually get valid information about that that could
11 help us for future drug design questions.

12 DR. ANTHONY: Thanks for the question, but I
13 think there I might have been misunderstood because for
14 reasons you probably know, I don't usually ask people
15 why they do things because I don't usually believe the
16 answer.

17 DR. WALSH: Well, that's why I'm asking
18 because I think it's important to know why here because
19 there's a lot to be learned from it.

20 DR. ANTHONY: Yes.

21 DR. WALSH: So, how do we construct that to--

22 DR. ANTHONY: No, I think it's a great

1 question, but this isn't the guy to answer that question
2 because I don't study things like that, but there are
3 people who do in the social psychology realm,
4 ethnography, anthropology, and so on.

5 DR. WALSH: Well, I mean, the question is not
6 the existential why, it's really why with this
7 medication, why would you continue to use the original
8 product of OxyContin and why did you not determine that
9 you would use it a second time? What were the barriers?

10 DR. ANTHONY: You're asking great questions,
11 but you're looking at a large sample, shallow,
12 quantitative epidemiologist. And you need someone who
13 has a little bit more depth in terms of what's going to
14 be probed into the answer to that question. And there
15 may be someone in the room, but it's not going to be me.

16 DR. WALSH: Well, let me ask you the second
17 question because I think that this one you probably have
18 thought about. So, it wasn't until, I think, the last
19 presentation from Dr. Keeton that someone raised the
20 fact that we really need to be thinking about the
21 relative risk or abuse, misuse versus exposure, and one
22 measure of exposure is sales, and it's very possible

1 that as a new product rolls out that is abuse-deterrent
2 that the sales are going to fluctuate, and that's a
3 changing background, and I'm wondering if you could just
4 say a few things about how to control for those changing
5 things.

6 And then the other thing that I started
7 thinking about was how would sales change? Let's say
8 that something really is successfully abuse-deterrent,
9 if you just in a very simplistic model think that
10 there's two categories of sales, and there's more than
11 that, obviously, but one is for legitimate patients and
12 then one is for the pseudo patients who are getting
13 legitimate prescriptions, but then are misusing it or
14 selling it.

15 You'd expect that those two pockets of sales
16 would really be differentially affected once it was
17 determined that the drug was abuse-deterrent and had a
18 lower street value, for instance. So, how do you
19 control for those factors in the background as we go
20 forward?

21 DR. ANTHONY: Okay, so, I think I have to
22 introduce three ideas.

1 One of them is that with respect to the last
2 point about the heterogeneity and the consumer
3 population, econometricians and economists have great
4 models for that heterogeneity. And whether someone is
5 buying the Volvo for safety considerations or because of
6 its looks or because it used to be from Sweden, I mean,
7 those are human behavioral economic modeling of the type
8 that Dr. Bickel was mentioning is really appropriate
9 there, but I don't think it's ever been applied in the
10 context of do FDA-type regulation of drug products.

11 Working backward toward the sales, I've always
12 really been a critic of using the sales as a
13 denominator when gauging event outcomes like the number
14 of overdoses and so on because the sales, as you just
15 pointed out, are a manifestation of demand of the drug.
16 Again, what you really require here is a multivariate
17 model, not a simple ablative ratio that is going to
18 destroy information that's contained in the sales and in
19 the event rate values.

20 So, I think the answer there is a multivariate
21 model where you're modeling sales; at the same time,
22 you're modeling outcomes sometimes with a lag that will

1 take into account that some of the outcomes are being
2 determined by a product that's been sitting in that
3 medicine cabinet for 6 to 12 months or more, and then
4 finally is getting out into a consumer pool that it
5 otherwise shouldn't get into.

6 And then back to the exposure question, you
7 know I love to ask people about if they've had a chance
8 to try a drug, and I would think with these new
9 products, knowing transition probabilities from having a
10 chance to try, and you could actually show them a
11 picture of the pill and whether they've actually used,
12 that transition probability is a really important one.
13 one might expect that a product that's favorable, that's
14 protective will have a longer lag time between chance to
15 try and actual use as compared to one that has a
16 reputation on the street as being the greatest thing
17 since sliced bread.

18 Okay, thanks.

19 DR. KIRSCH: Okay, so, next, we're going to
20 get to the presentation of the Sponsor.

21 Both the Food and Drug Administration and the
22 public believe in a transparent process for information

1 gathering and decision making. To ensure such
2 transparency at the Advisory Committee Meeting, the FDA
3 believes that it is important to understand the context
4 of an individual's presentation.

5 For this reason, FDA encourages all
6 participants, including the Sponsor's non-employee
7 presenters, to advise the Committee of any financial
8 relationship that you may have with the firm at issue,
9 such as consulting fees, travel expenses, honoraria, and
10 interest in the sponsor, including equity interests and
11 those based upon the outcome of today's meeting.
12 Likewise, FDA encourages you at the beginning of your
13 presentation to advise the committee if you do not have
14 any such financial relationships. If you choose not to
15 address this issue of financial relationships at the
16 beginning of your presentation, it will not preclude you
17 from speaking.

18 There's been in a change in the organization
19 of the presentation by Purdue. So, I'll announce each
20 speaker as they come up. The first speaker is Dr.
21 Landau.

22 **Industry Presentation: Purdue**

Introduction

DR. LANDAU: Thank you. Good afternoon. I'm Craig Landau, Purdue's chief medical officer. On behalf of our company, I want to thank the Agency and the combined advisory committees for the opportunity to present and share with the group our Epidemiologic Study Program. We believe and hope we'll shed light on whether or not we've been successful and to what degree we've been successful on effecting abuse and it's consequences with the reformulation.

We've used reformulation science to lessen OxyContin's attractiveness to abusers, while retaining the benefits intended for patients. We reformulated OxyContin in such a way that we view it as a risk mitigation tool to deter its abuse. And we certainly recognize the role OxyContin has played. It's a vulnerability in the ease with which it could be crushed and how attractive that feature has made it to abusers. So, we're very happy to be here today to attempt to learn how to do something about that and measure it. The reformulation was approved earlier this year, and we're actually in the midst of transitioning to the new

1 formulation as we speak.

2 Following my introduction, we'll provide an
3 overview and sort of a description for our rationale in
4 designing this eight-study program. We'll then move
5 into a presentation of individual studies, a detailed
6 presentation. The Chairman, Dr. Kirsch, has done me a
7 favor by notifying everyone that the agenda, the
8 sequence of the presentations is different from the
9 original agenda, but the slides that have been provided
10 to you are in the correct order. So, following the
11 individual study presentations, we'll conclude by
12 summarizing and offering some closing remarks.

13 Before the scientific presentations begin,
14 I'll speak to four topics: our rationale for
15 reformulating the product, the transition to the new
16 formulation, our thoughts on how formulations intended
17 to deter abuse should be characterized, and our position
18 on label claims for abuse deterrence.

19 Millions of patients have been treated with
20 OxyContin since it was approved in 1995. And while safe
21 and effective when used appropriately by legitimate
22 patients, we recognize the original formulations

1 controlled-release delivery system could be easily
2 crushed, easily defeated. Within seconds, an abuser
3 with no more than two spoons or a bottom of a beer
4 bottle could defeat the controlled-release delivery
5 system and convert a controlled-release, twice-daily
6 product to an immediate-release dose form of oxycodone.
7 The result in material could then be swallowed, snorted,
8 or even injected. So, we reformulated the product for
9 the purpose of reducing or addressing this vulnerability
10 and reducing its abuse.

11 The next few slides provide a visual
12 impression and highlight some of the features between
13 the original formulation and the reformulated medicine.
14 And, as you can see here, the two formulations are
15 similar in appearance, but not identical. The most
16 obvious difference is in the indicia. The original
17 tablet on the top of the slide, displaying an OC
18 indicia, and the reformulated product on the bottom
19 displaying OP.

20 And, like most strengths of the formulation,
21 including the 40 mg tablet represented here, most of
22 them are slightly larger and slightly thicker than the

1 original formulation.

2 But, despite their similar visual appearance,
3 the formulations have very different physical chemical
4 characteristics. The original formulation on the top
5 half of the slide can be converted to a fine powder in a
6 matter of seconds, as I've mentioned. The reformulated
7 tablets require much more effort, much more time, and,
8 in some cases, specific tools and energy to reduce the
9 tablets into smaller particle sizes. We understand from
10 our experience that inadvertent misuse by patients and
11 intentional abuse by abusers often, but not always,
12 starts with attempts to manipulate the tablet.

13 Of course, the image on top is the original
14 formulation, crushed between two spoons. You can see a
15 final powder. On the bottom half of the slide, a
16 reformulated tablet that contains the same tablet
17 strength after five minutes of vigorous manipulation in
18 a mortar and pestle. And you can see large tablet
19 fragments there.

20 When mixed with a volume of water-soluble for
21 intravenous injection through a tuberculin or an insulin
22 syringe, the original tablet, when hydrated, is easily

1 drawn up and easily injected. It's what makes it so
2 very attractive to those who seek to abuse it via the
3 intravenous route. The reformulated tablet, on the
4 other hand, becomes quite viscous, difficult to syringe
5 or draw up into a syringe, if not impossible to draw up
6 and inject using commonly-available syringes, 27 or
7 higher gauge needles.

8 These are the properties we introduced into
9 the tablet to make them more difficult to manipulate and
10 less attractive to abusers. It was specifically
11 designed to deter crushing, snorting, and intravenous
12 injection. It's bioequivalent to the original
13 formulation, and, therefore, it's considered
14 therapeutically interchangeable for patients. The
15 Agency approved the reformulated product on April 5 of
16 this year, and we're in the midst, as I mentioned a
17 moment ago, of the transition to the reformulation.
18 Our goal is to do this as quickly as possible to reduce
19 confusion, reduce overlap of the two formulations, but
20 to do it not at the expense of patient access. We
21 understand the concept of physical dependence, and want
22 to avoid a condition where a patient would go to a

1 pharmacy to fill their prescription and not be in a
2 position to receive one. This could become a safety
3 issue. So, with over 1.2 million patients treated
4 annually, this transition is quite significant.

5 Here on this slide, we see a plot of weekly
6 prescriptions dispensed for OxyContin at retail
7 pharmacies. In the yellow color, we see the original
8 formulation over time starting in June of this year, and
9 in the orange color, the reformulated OxyContin product.

10 A few things to point out here. We stopped
11 shipping the original formulation on Thursday, August 5,
12 and we began to ship exclusively to wholesalers the
13 reformulated product on Monday, August 9. As of October
14 1, the only formulation a retail outlet could obtain
15 from a wholesaler was the reformulated product. So, at
16 the wholesaler level, the supply chain was saturated
17 with only reformulation.

18 For the week ending October 1, 65 percent of
19 all OxyContin prescriptions dispensed were for the
20 reformulation, and, in fact, at the break, I just
21 learned that within the week ending October 8, that
22 number is now 70 percent. By the end of this month, we

1 expect it to approximate 90 percent, and sometime before
2 or at or about the end of the year, we expect the
3 transition to be nearly complete at the patient level.

4 So, in order to characterize its potential
5 abuse, we worked with the Agency, Abuse Surveillance,
6 and drug safety experts to develop what we think is a
7 very rational, four-step plan, much like the plan or
8 approach described earlier today included in certain
9 guidance documents and referred to by Dr. Rappaport in
10 his memorandum to the combined advisory committees.

11 The first step is *in vitro* testing in a
12 laboratory, and where we look to define the physical
13 chemical properties of the formulation and go further to
14 define its failure limits. Now, we've done that, of
15 course, and the data was the subject of discussion at
16 the September 2009 meeting of these combined advisory
17 committees.

18 Our experiments were designed by external
19 experts in abuse and extraction, and the experiments
20 were designed to reflect methods that abusers currently
21 and could use to defeat a controlled-release delivery
22 system. The large majority of the experiments were done

1 on the outside through third-party CROs to reduce
2 potential bias. The data were QAed and then interpreted
3 on the outside, as well, by experts.

4 The results of the studies, for those not
5 familiar, suggest the reformulation to be more difficult
6 to purposefully or inadvertently crush. Certainly more
7 difficult to insufflate if one does to abuse by
8 intravenous injection. That it doesn't dose dump in the
9 presence of alcohol, and that it's inefficient to abuse
10 by smoking.

11 The second level of testing, pharmacokinetic
12 testing, is fairly straight forward. We looked to
13 determine the bioavailability of the intact tablet and
14 tampered tablets along with relevant controls in the
15 volunteer setting.

16 Studies on the third level, abuse liability,
17 go one step further, and looked to introduce subjective
18 measures or an evaluation of subjective measures.
19 Again, alongside pharmacokinetics, studying intact and
20 tampered reformulated OxyContin and relevant controls.

21 So, the *in vitro* data were submitted to the
22 NDA. They were discussed and reviewed by the Agency,

1 discussed at the Advisory Committee in September of last
2 year. The testing on levels two and three were recently
3 completed and submitted to the division for review.
4 Each of the levels, the first, second, and third level,
5 as mentioned earlier this morning, are informative for
6 sure, but they're insufficient to predict what will
7 happen when a product is introduced in a real-world
8 setting. To do this, post-marketing outcome data are
9 needed, and these studies comprised the fourth level of
10 testing, epidemiologic testing.

11 Purdue believes all newly-approved opioid
12 products should possess some degree of abuse-deterrent
13 features, whether they be pharmacologic or physical
14 chemical. And all such products should undergo testing
15 on each one of these four axes at the relevant time in
16 their development.

17 The testing performed to date with the
18 reformulated OxyContin product tells us it's an
19 incremental improvement over the original formulation
20 with respect to its resistance to manipulation. But new
21 formulations are not a complete solution. We understand
22 that prescription drug abuse is complex, it's a multi-

1 factorial problem, and it can't be solved simply by
2 addressing a defect in a single formulation, that is the
3 ease with which OxyContin product could be crushed and
4 its controlled-release delivery system defeated. Or by
5 introducing a new product. Our reformulation will still
6 be abused whether by swallowing intact tablets or after
7 tampering, after an abuser looks to spend the required
8 time and effort to manipulate the tablet.

9 Nonetheless, transitioning to the
10 reformulation as we did, or as we begun in August,
11 represents an opportunity to make a positive impact, and
12 that's what we're here to do. Understanding the impact
13 of the formulation requires diverse approaches, and
14 that's what this meeting is about.

15 The transition and the unprecedented challenge
16 of designing the studies we're discussing provides us a
17 unique opportunity. It's an opportunity to research and
18 to measure if and how a change in a formulation can
19 impact a clinical outcome. I don't know that we've had
20 this opportunity before.

21 We've also learned that no single
22 epidemiologic study can adequately assess the impact a

1 formulation can make. We're hopeful that the eight
2 studies, the multi-study program we've proposed will
3 give us a lens and help us to understand if and how one
4 can be successful; we or other Sponsors.

5 We're pursuing the studies to meet a post-
6 marketing requirement issued to Purdue as an approval
7 requirement, and, of course, to learn what impact, if
8 any, a formulation could have on abuse and its
9 consequences. We did not design these studies with the
10 goal of pursuing a label claim, and we're not currently
11 seeking one.

12 Given the complexities of the studies and the
13 context in which we're discussing them, we feel a
14 conservative approach to both interpretation and
15 communicating the results of the study is warranted. We
16 start with an assumption that within the class or within
17 a given schedule of drug, the abuse liability of all the
18 products should be considered the same or similar. Any
19 claim of reduced abuse liability must be based on
20 substantial, sustained, and consistent effects measured
21 over time in a real-world setting on a number of axes of
22 evaluation. We understand the complexities and the

1 interrelationships of some of the outcomes we're going
2 to be presenting in a few minutes.

3 Even if the evidence is deemed sufficient to
4 support a label claim at some point going forward, there
5 were risks to making one. We heard some of the speakers
6 this morning talk about them. For one thing, and
7 members of this panel and previous meeting have
8 surfaced, creating a false sense of security in the
9 minds of prescribers, dispensers, and patients is
10 something we'd look to avoid. It could introduce or
11 cause reduced vigilance. Reduced vigilance could
12 eliminate or at least reduce any of the potential
13 benefits of formulation like our reformulation could
14 introduce, and it could certainly undermine the goals of
15 the class REMS currently under consideration within FDA.

16 I said more plainly reduced vigilance could
17 worsen the already significant public health crisis we
18 spoke about this morning, that of prescription opioid
19 abuse and prescription drug abuse, something we wish to
20 avoid. If we, in the future, or any sponsor does
21 generate a level of convincing evidence substantial and
22 sustained and consistent across axes, I think at that

1 point, we would hope that we press pause and a benefit
2 risk assessment be made. We'd want to be as certain as
3 we can that the benefits of introducing language in a
4 product's label offset the risk we talked about in the
5 context of the larger public health.

6 To help us design and understand the results
7 of the studies we'll be presenting in a moment, we've
8 enlisted the help of outside experts. A couple are here
9 with us today, and you'll from Dr. Richard Dart in a
10 moment. The experts are listed here, Dr. Elizabeth
11 Andrews, Dr. Greg Burkhardt, and Dr. Richard Dart, Dr.
12 Ken Rothman, and Dr. Ed Sellers.

13 In a moment, we'll move forward with the
14 agenda. You'll hear from Dr. Paul Coplan next. He's
15 Purdue's new head of Risk Management in Epidemiology.
16 He's also an adjunct assistant professor at the
17 University of Pennsylvania School of Medicine in the
18 Department of Clinical Biostatistics in Epidemiology.

19 Paul will provide the overview and the
20 rational for the eight-study program.

21 Following Paul, five external experts and one
22 internal expert, Dr. Howard Chilcoat, who's new to

1 Purdue, will go through each of the individual studies
2 in more detail. Prior to joining Purdue, Howard was an
3 associate professor at Johns Hopkins Bloomberg School of
4 Public Health, and was also chief of the epidemiology
5 research branch at the National Institute on Drug Abuse.
6 And when we conclude the study presentations, Paul will
7 come back with some concluding remarks and direct
8 responses to any questions the committee or anyone has
9 on our work.

10 Thank you.

11 **Overview and Rationale of Study Program**

12 DR. COPLAN: Thank you, Dr. Landau. Good
13 afternoon. Thank you for the opportunity to address
14 this committee. The purpose of this presentation is to
15 provide an overview and rationale for the Epidemiologic
16 Study Program that Purdue plans to conduct to assess the
17 effect of the new formulation on abuse. This program is
18 designed to meet FDA's requirements for post-marketing
19 studies. We very much appreciate the insight of the
20 FDA, members of the Advisory Committee, and other
21 experts to ensure that the studies answer the most
22 important public health questions about the new

1 formulation, particularly in the light of the
2 limitations of each of the available data sources that
3 we heard about earlier today.

4 In order to evaluate the effects of a new
5 formulation on the epidemiology of prescription opioid
6 abuse, it is important to first characterize the
7 background epidemiology of prescription opioid abuse and
8 its adverse consequences. For each of the upcoming
9 presentations, we have worked to provide the relevant
10 background epidemiology so that you can evaluate the
11 relevance of the study designs, the study populations,
12 and the outcome measures. This background epidemiology,
13 including baseline data, may also assist in predicting
14 the hypothesized effect of the new formulation.

15 OxyContin is the extended-release formulation
16 of oxycodone. The extended-release system of the
17 original formulation was easily circumvented by
18 crushing, breaking, or dissolving. And to address an
19 earlier question by Dr. Omoigui, this is crushing the
20 tablet and dissolving it for purpose of snorting or
21 injecting.

22 A characteristic of oxycodone in general, and

1 extended-released oxycodone in particular, is the
2 diversity of routes by which it is popularly abused. We
3 get a baseline picture of these routes of abuse from the
4 National Surveillance System of 500 abuse treatment
5 centers around the U.S. In the past 3.5 years, more
6 than 7,000 people who enter treatment in one of the 2
7 centers of the network reported abusing OxyContin during
8 the intake clinical examination by at least 1 of 4
9 routes. Snorting was the most common route of abuse,
10 and 34 percent reported abuse by injecting. These
11 numbers don't add up to 100 percent because subjects
12 could endorse more than one route of abuse, as Dr.
13 Paulozzi referred to earlier.

14 Other frequently-abused opioid drugs have
15 fewer primary routes of abuse. For example, people
16 primarily abuse hydrocodone via the oral route and abuse
17 morphine through injecting, as we'll see in a later
18 presentation by Ms. Cassidy.

19 Oxycodone's diversity of route of abuse may
20 have increased its popularity among people who initiate
21 abuse via the oral route and who progress to more
22 frequent abuse via injecting and snorting.

1 This pattern is reflected in data from a study
2 of people abusing OxyContin in Kentucky. Located in the
3 Appalachian region that has one of the highest rates of
4 death from opioid overdoses in the U.S. It looks at
5 people entering a treatment program of an average of
6 19.7 months of abusing the drug. The left bar shows the
7 initial route of administration when they started
8 abusing OxyContin and is based on the medical chart
9 information.

10 The right bar shows the stated routes of
11 administration upon admission to the treatment center.
12 There were substantial shifts in the routes of abuse
13 after 19 months of abusing. Snorting increased from 16
14 percent to 58 percent and injecting increased from 1
15 percent when initiating abuse to 21 percent upon
16 treatment admission. These data provide one example of
17 how routes of abuse can change as the stages of abuse
18 progress and suggest the likely benefits the
19 reformulation may provide.

20 For legitimate users, the hypothesized benefit
21 is to provide bioequivalent delivery of oxycodone to
22 treat moderate to severe pain while reducing the

1 inadvertent areas in usage that the patients and nursing
2 staff sometimes commit through breaking, crushing, or
3 chewing of OxyContin, which was previously referred to
4 by the FDA definitions as misuse. To date, 155 cases of
5 OxyContin overdose associated with such areas have been
6 reported to the Purdue Case Report Database.

7 For abusers of OxyContin, the hypothesized
8 benefits if the physical chemical properties of the
9 reformulation impede tampering are reduction in abuse
10 through breaking, crushing, or chewing due to the
11 tablet's hardness. Injecting will be reduced due to the
12 hydro-gelling of the tablet when dissolved in water, as
13 Dr. Landau mentioned earlier, snorting will reduced due
14 to properties of the new formulation tablet that, when
15 crushed, they crumble into large chunks rather than a
16 fine powder created by crushing the old formulation, and
17 the large chunks form a gel in the nasal passages. FDA
18 is requiring measurable endpoints for the epidemiology
19 studies. The hypothesized benefits need to be mapped to
20 these endpoints.

21 In FDA's background document for this meeting,
22 FDA stated future studies need to address abuse and

1 misuse and its consequences, overdose, addiction, and
2 death. To measure the impact on abuse and misuse, the
3 potential impact of the new formulation can be studied
4 by assessing changes in the prevalence of abuse, demand
5 for purposes of abuse, and abuse via routes of
6 administration that require tampering.

7 It is possible that reducing abuse via routes
8 that require tampering may have a downstream benefit of
9 reducing the clinical outcomes of abuse, including
10 overdose, addiction, and death. These are what FDA has
11 referred to as the consequences of abuse. We have been
12 tasked with designing epidemiology studies that will
13 measure the effects of the new formulation.

14 Because of the multifaceted nature of the
15 prescription opioid abuse problem in the overall
16 community, no single study could assess all the aspects
17 of the problem, such as the subpopulations affected, the
18 influence of routes of administration, and the stages of
19 addiction that we heard in the discussion by Dr. Anthony
20 earlier. Each of the studies have specific strengths
21 and limitations relating in part to the strengths and
22 limitations of available data sources. As a result, we

1 engaged a panel of experts to help us design multiple
2 studies to measure the different aspects of the problem.
3 based on the input, we've developed a program of studies
4 designed to comprehensively measure the effects of the
5 new formation. The individual studies will provide
6 collaborating evidence of the real-world effects across
7 studies and multiple data sources. Taken together, the
8 totality of the program is designed to leverage the
9 strengths and address the limitations of the individual
10 studies.

11 The key questions that we will be seeking to
12 address in these eight studies will be based on these
13 design principles. The first question is, and this
14 could be phrased as a question or a hypothesis, is:
15 Will the methods for tampering and extraction become
16 widespread? We know that certain routes of abuse will
17 be developed, but if they require too much effort and
18 are too burdensome, they're unlikely to become
19 widespread.

20 Is the reduction in abuse via routes that
21 require tampering? Is there a reduction in abuse in the
22 community? Is the reduction in demand for purposes of

1 abuse? And, lastly, and most importantly, is there a
2 reduction in clinical endpoints, including in specific
3 subpopulations of pain patients, the general population,
4 and the people entering treatment for addiction? These
5 questions will then be matched to specific studies to
6 address the questions.

7 The Internet discussion will be conducted to
8 address the first question. A study of an abuser cohort
9 in Kentucky and surveillance of addiction treatment will
10 be conducted to address the second question. Surveys,
11 such as the NSDUH, and other surveys will be conducted
12 to assess the third question. Law enforcement in the
13 RADARS System and doctor shopping and Prescription
14 Monitoring Programs will be conducted to assist the
15 fifth question.

16 And lastly, the Kaiser Overdose Study and the
17 Poison Center Program--the Kaiser Overdose Study will be
18 conducted to assist outcomes in pain patients. To
19 assist outcomes in the general population, the Poison
20 Center Program, and, in addition, the Kaiser Overdose
21 Study will be used. And, lastly, to monitor changes in
22 routes of abuse and types of abuse in people entering

1 treatment for addiction, we'll be using a study of
2 surveillance of addiction treatment centers.

3 A table showing the eight studies and the
4 outcomes they're designed to measure would be helpful
5 for summarizing the program. This helps to see that the
6 eight studies cover the outcomes that FDA is requesting
7 to be addressed. I should mention that in produced
8 background document for this meeting, only seven studies
9 were listed. We added an eighth study, a study of law
10 enforcement event in the RADARS System. This study was
11 added because when we were preparing for this meeting,
12 some external experts told us that a study of law
13 enforcement events would be helpful. Since Purdue was
14 already conducting such a study as part of an ongoing
15 risk management activity, we added this to the study
16 program.

17 The duration of baseline data for each of
18 these studies will be relevant to the ability of the
19 studies to measure changes over time, and we'll be
20 coming back to this slide repeatedly and using it as a
21 structure for organizing each of the eight studies so
22 that the eight studies don't seem like a morass of

1 diffused studies, but that their purpose in measuring
2 specific outcomes is apparent or hopefully apparent.

3 The duration of the baseline varies from 6
4 months for the abuser cohort in Kentucky to 7 to 8 years
5 in the Drug Diversion Study, and the Poison Center
6 Study, in 10 years in the Kaiser Overdose Study. All of
7 the studies already collecting the data needed for
8 validating the effect of the new formulation.

9 For the Poison Center and Drug Diversion
10 Programs, Purdue has been receiving quarterly reports
11 from the Rocky Mountain Poison Center and will continue
12 to get these in an ongoing fashion, and Dr. Rick Dart
13 will present more on that in a moment.

14 The Kaiser data is an Electronic Medical
15 Record System that collects data on patients using
16 OxyContin in an ongoing way. So, as we speak, the
17 endpoints for the study are being collected.

18 The time to see an effect for the new
19 formulation, we estimate, will vary depending on the
20 nature of the endpoint that the study's designed to
21 detect. It'll take six to nine months for studies that
22 measure routes of abuse, according to our best estimate,

1 one to two years to see an effect for studies that
2 measure changes in usage and demand, and one to two
3 years, probably closer to two years, to see an effect
4 for studies that measure changes in clinical outcomes.
5 The planned analysis must take into account the baseline
6 trend, the pre post changes, and compared to comparator
7 drugs, as was mentioned earlier by the FDA speaker.

8 The planned analyses will use an interrupted
9 time series approach where baseline trend is identified,
10 a change shortly after the introduction of the new
11 formulation is evaluated, and, secondly, the trend over
12 time after the introduction of the new formulation is
13 evaluated. The changes in trends will be assessed for
14 OxyContin as well as for comparator opioids.

15 The depiction on this slide is one of the ways
16 in which we hypothesize success will look. A change in
17 the trend for OxyContin, but not for other comparator
18 opioids. It is important to select comparator
19 prescription opioids that can capture background trends
20 in abuse of prescription opioids.

21 Immediate-release oxycodone provides a close
22 comparison to OxyContin since they share a common active

1 drug substance and only different extended-release
2 mechanism versus the immediate-release formulation.
3 Hydrocodone combinations are one of the most frequently
4 prescribed and abused types of opioids in the U.S., and,
5 therefore, provides a relevant comparator.

6 Extended-release opioids, such as extended-
7 release morphine sulfate, excluding naltrexone-
8 containing formulations, and the fentanyl transdermal
9 patch provide a useful comparator since they are
10 indicated for the same indication as OxyContin. In
11 addition, these comparators are also included with class
12 REMS for longer-acting opioids. So, they provide a
13 control for the background effects of the class REMS.

14 Lastly, methadone will be used as a comparator
15 because in many mortality studies, methadone, at least
16 in the past, did appear as the number one cause of
17 opioid overdose deaths.

18 As an example of why it is important to
19 measure background trends and comparator opioids,
20 changes in immediate release or I'll call them IR, and
21 extended releases, or ER oxycodone are relevant.

22 Over the past 10 years, there have been large

1 shifts in prescribing practices for extended-release
2 oxycodone and immediate-release, single entity oxycodone
3 that must be considered when utilizing immediate-
4 release, single entity oxycodone as a comparator. This
5 data from SDI looking at retail prescriptions shows that
6 there's been a 40 percent rise in the number of
7 prescriptions for extended-release oxycodone from 5.5
8 million prescriptions in 2000 to 7.7 million
9 prescriptions in 2009.

10 In the same time period, there's been a 660
11 percent rise in the number of prescriptions for IR
12 single entity oxycodone from 1.2 million prescriptions
13 in 2000 to 9.2 million prescriptions in 2009. The
14 source of the data is the FDA's Advisory Committee
15 Briefing Document from the last advisory committee of
16 this group.

17 In selecting a comparator, it is also
18 important to differentiate between immediate-release
19 single entity oxycodone and immediate-release
20 combination oxycodone. Ninety-nine percent of the
21 immediate-release combination of oxycodone prescribed in
22 the U.S. is for oxycodone-acetaminophen combinations.

1 Data from the DAWN study that the FDA
2 presented to this advisory committee on April 22 show
3 that the risk of emergency department visits for non-
4 medical use using a denominator of 10,000 prescriptions
5 that was obtained from the SDI data show that there's
6 substantially different risk of ED visits for immediate-
7 release single entity oxycodone, which is shown in the
8 violet line and immediate-release oxycodone in
9 combination shown in the green line.

10 In 2008, the risk of overdose at adverse
11 events was substantially higher for immediate-release
12 single entity oxycodone than for IR oxycodone
13 combination. Forty-five versus thirteen per ten
14 thousand prescriptions respectively. And between 2004
15 and 2008, the risk of overdose adverse events was 20
16 percent for ER oxycodone, 62 percent for IR oxycodone
17 combined, and 150 percent for IR oxycodone single
18 entity. It would be important to take these background
19 trends into account when designing studies and
20 interpreting the results. Data systems that do not
21 differentiate whether the cause of overdose or death is
22 due to IR or ER oxycodone could thus mass-effect with

1 tamper-deterrent formulation.

2 This overview and rationale provides a context
3 for the presentation of the individual studies. The
4 first study utilizes the existing Electronic Medical
5 Records System of the Kaiser Permanente Health System
6 that records overdoses and poisonings due to opioids.
7 If the new formulation is successful, this study will
8 demonstrate reductions in the instance rate of OxyContin
9 overdoses and poisonings per prescriptions for OxyContin
10 amongst the membership of the Kaiser population. The
11 first study will be presented by Dr. Nancy Perrin, who's
12 a senior investigator at Kaiser Permanente Northwest in
13 Portland, Oregon.

14 **Overdose Rates in OxyContin Patients and Non-Patients at**
15 **Kaiser Permanente**

16 DR. PERRIN: Good afternoon. I'm Nancy
17 Perrin, a senior investigator at the Center for Health
18 Research at Kaiser Permanente Northwest. My area of
19 expertise is biostatistics and research design.

20 Prior to coming to the Center, I was professor
21 and director of the Statistical Corps in the School of
22 Nursing at Oregon Health and Science University. I have

1 no personal financial interests in the outcome of this
2 meeting, and I have been paid by Purdue for my time.

3 I am leading this study, exploring the rates
4 of adverse events in OxyContin patients and non-patients
5 at Kaiser Permanente. The study is particularly
6 relevant because it focused on clinical outcomes in a
7 broad population. We have 10 years of Electronic
8 Medical Records to establish the trend and adverse
9 events prior to the introduction of the new formulation.
10 The study will provide data on the impact of the new
11 formulation on opioid-related adverse events reported
12 within the Kaiser Permanente System.

13 We have already gathered data to determine the
14 baseline trend. This is our initial estimate of opioid-
15 related poisonings in Kaiser Permanente Northwest from
16 1998 to 2009. We identified poisonings and linked those
17 with opioid dispensings in the six months prior to the
18 event.

19 The graph shows the number of poisonings among
20 people with various dispensings of opioids. OxyContin
21 and extended-release oxycodone are shown in orange,
22 immediate-release oxycodone in pink, and other Schedule

1 II opioids in yellow.

2 The trend in the poisonings is increasing over
3 time for all the groups, which increases our power to
4 detect a change with a new formulation. Interestingly,
5 many of the opioid-related poisonings are among patients
6 that did not have a dispensing of any opioid in the six
7 months prior to the adverse event, as shown in the blue
8 line here at the top of the graph. These are likely
9 people who are intentionally misusing opioids.

10 As Dr. Coplan mentioned, we are continuing to
11 assess adverse events since the introduction of the new
12 formulation. The objective of our study is to assess if
13 the rate of overdose adverse events associated with
14 OxyContin decreases with the new formulation. The
15 population for this study are Kaiser Permanente Health
16 Plan members, both with and without dispensing of
17 opioids. Using a cohort study, we'll examine poisoning
18 and overdose adverse events derived from Electronic
19 Medical Records. We have 10 years of baseline data, and
20 it will take 2 years after the introduction of the new
21 formulation of OxyContin to determine its effect.

22 Kaiser Permanente, or KP, as we like to call

1 it, has multiple regions, many of which will be included
2 in our study. The pilot work is being conducted at the
3 KP Northwest, which has over 475,000 members annually
4 and will guide the scale of the full study.

5 For the full study, we have access to data
6 from over 8 million members across the regions of KP.
7 The regions are linked by the Virtual Data Warehouse,
8 which is a unique data resource that combined
9 comprehensive membership, demographic, in-patient
10 utilization, outpatient utilization, dispensed
11 prescriptions, laboratory tests, and imaging data dating
12 back to 1996 from multiple health plans. It's derived
13 from Electronic Medical Records, not insurance claims.

14 The KP population and the Virtual Data
15 Warehouse provide us with an opportunity to also examine
16 adverse events among family members of patients
17 dispensed opioids. We will identify family members of
18 individuals with dispensings of opioids and conduct
19 separate analyses for this sub-sample. This is a unique
20 opportunity to examine accidental use and misuse of
21 OxyContin.

22 As I mentioned, we are studying the trend in

1 adverse events over time. We plan to compare cohorts
2 with dispensings of different opioids, as Dr. Coplan
3 mentioned, with an interrupted time series approach.
4 The interrupted time series design is an optimal method
5 for conducting naturalistic studies of the effect of
6 system level changes, such as the introduction of the
7 new formulation of OxyContin. This approach compares
8 the trend over time and the rate of adverse events
9 before and after the introduction of the new
10 formulation. As we begin to observe the trend forward,
11 we can test if it follows the same path as the baseline
12 trend or if there has been a significant change in the
13 trend.

14 Critical to the validity of the study is the
15 proper identification of adverse events in the
16 Electronic Medical Records. Adverse events can be
17 derived from ICD-9 and 10 codes. These events can be
18 classified as poisonings or overdoses. To be sure that
19 we are capturing changes in the use of the ICD codes
20 over time, we are currently conducting chart audits to
21 examine patterns of codes used to document opioid-
22 related adverse events in the KP Northwest System.

1 Additional audits are being used to validate our
2 algorithms to extract adverse events from the Electronic
3 Medical Records.

4 The analysis is based on rates of adverse
5 events. We will actually look at multiple rates. The
6 first is the rate of OxyContin-related adverse events
7 for which the numerator is the number of adverse events
8 among patients prescribed OxyContin and the denominator
9 reflects the extent of the use of OxyContin. The rate
10 will be calculated for each time period in the time
11 series and compared to rates of adverse events among
12 patients prescribed other opioids. We will compute
13 comparator rates for OxyContin immediate release and
14 other Schedule II opioids, and we can vary these
15 denominators to capture different subpopulations such as
16 people with new prescriptions of opioids.

17 Comparing the rates allows us to control for
18 changes in the number of members and prescribing
19 patterns across time. Regression will be used for the
20 statistical analyses. The model we will use yields
21 unbiased estimates of the level and slope of the trend
22 in the adverse events prior to the introduction of the

1 new formulation to the left of the dotted line here and
2 estimates of the change in the level and slope after the
3 introduction of the new formulation.

4 The change in level provides an estimate of
5 the immediate effect. The change in slope provides an
6 estimate of the difference in the trends between the two
7 time periods.

8 The main comparison is between the slope of
9 the trend prior to and post the new formulation. This
10 means that statistical power of the study is a function
11 of the change in slope. Long, stable baseline periods
12 provide greater statistical power to detect changes
13 after the implementation of the new formulation. And
14 rates based on large sample sizes and the same
15 populations over time improve stability. The multiple
16 regions of KP provide very large populations to estimate
17 these trends.

18 In our pilot work, we have observed in KP
19 Northwest over 580 opioid-related poisonings per year in
20 recent years, and estimate there will be approximately
21 125 to 150 additional overdose events per year. We have
22 calculated preliminary estimates of power based on the

1 pilot data for poisonings in KP Northwest.

2 We are still working on our algorithms to
3 extract overdose events. Approximately 1 percent of
4 patients in KP Northwest with dispensings of OxyContin
5 has a poisoning event. We calculated the number of
6 patients needed to detect various degrees of change from
7 the two years prior to the new formulation to the year
8 after the introduction of the new formulation.
9 Approximately 3,600 patients are needed to detect a 50
10 percent reduction in the rate of poisonings and with 80
11 percent power, and approximately 4,800 patients with 90
12 percent power. These are preliminary, conservative
13 estimates of power as they were based on comparisons of
14 two rates, not the differences in the slope of the
15 trends over time, and they were based on poisonings
16 only.

17 The main power analysis will be conducted when
18 we conclude our pilot work, and we'll use simulations
19 approaches to determine the sample size needed to detect
20 various changes in slopes. Based on these power
21 estimates, we'll determine which KP regions to include
22 in the main study to assure an ample sample size.

1 One strength of our design is our ability to
2 statistically compare trends over time for different
3 opioids. Including comparator groups improves the
4 internal validity of our study. Differences in the
5 changes and trends over time between OxyContin and
6 comparator opioids can be tested by incorporating
7 interaction terms into the regression analyses. We
8 might find that there's no change in the trend of
9 adverse events pre and post the introduction of the new
10 formulation for either OxyContin or the comparator
11 opioid, as illustrated here. Or we may see a decline in
12 the rate of adverse events for OxyContin after the new
13 formulation is introduced, but not the comparator
14 opioid, as illustrated on the left.

15 Alternatively, there could be a decline in the
16 rate of adverse events for OxyContin and an increase in
17 the rate of adverse events for other opioids. The study
18 I have described today has its strengths and
19 limitations. The limitations of the design include the
20 fact that not everyone fills their prescriptions at KP.
21 However, we do know from previous work that less than 10
22 percent of prescriptions are filled outside of the KP

1 System. We may not always be able to identify the
2 opioid uniquely associated with an adverse event since
3 people can be prescribed more than one type of opioid,
4 especially to manage pain within the observation window.
5 The study does have a limited socioeconomic profile as
6 it is conducted in an insured population.

7 The strengths of the study include the ability
8 to incorporate a comparator time series of other
9 opioids, improving the internal validity of the
10 research. We have a 10-year baseline period from which
11 to detect changes in trends after the new formulation.
12 Use of data derived from Electronic Medical Records and
13 access to geographically diverse regions of KP through
14 the Virtual Data Warehouse are additional strengths of
15 the study.

16 Thank you.

17 DR. COPLAN: Thank you, Dr. Perrin.

18 Our next study, the second study, utilizes the
19 existing network of poison centers in the U.S. if the
20 new formulation is successful, this study will
21 demonstrate reductions in the number of OxyContin
22 exposures reported to poison centers over time. This

1 study will also assess whether the number of deaths from
2 OxyContin reported to poison centers declines as a ratio
3 of the number of reported exposures.

4 The presenter for this is Professor Rick Dart.

5 **Exposures Reported to Poison Centers**

6 DR. DART: Good afternoon, and thanks for the
7 opportunity to present to the committee and describe how
8 RADARS can be used to assess the new formulation of
9 OxyContin.

10 First, my disclaimer. I have no personal
11 financial interest in the outcomes of this meeting,
12 however, my travel expenses only were paid for by Purdue
13 for this trip.

14 I'd like to start with an overview of the
15 RADARS system. The idea here, of course, is we're
16 trying to understand prescription medication abuse and
17 misuse, and, as several speakers have said today, you
18 need to look at it from multiple perspectives because
19 these people rarely present themselves. So, the
20 principle behind RADARS is to do exactly that, is to
21 create a mosaic by looking at prescription medication
22 abuse from several different perspectives. We currently

1 have six different programs, and in response to one of
2 the comments made this morning, we actually have just
3 created the methodology and tested it to look at street
4 price of prescription opioids, as well, and we'll be
5 adding that program to the RADARS System.

6 Purdue and most of the manufacturers of
7 opioids use RADARS for their post-marketing commitments
8 and to perform risk management. Specifically for the
9 evaluation of OxyContin though, we're focusing on three
10 programs, and I'm going to talk about two of those
11 today. The first two you see here, which is the
12 criminal justice system through drug diversion and acute
13 events through the poison center.

14 First, the poison centers. The U.S. is very
15 fortunate, at least I think so, in that we have a system
16 of 60 poison centers across the country that cover every
17 part of the United States, and you can reach them
18 through a single toll-free number, the poison help
19 number, and that leads the caller to initial triage and
20 care advice for their poisoning or their exposure I
21 should say because not all of these are true poisonings.
22 That information, they're helped by a health care

1 professional, either a nurse or a pharmacist, and that
2 information is entered into a single database from all
3 poison centers. We all use the same fields, and that
4 software has certain data-checking elements to it to
5 make sure we don't enter pregnant males and that type of
6 issue.

7 Eventually, the patient receives a
8 disposition, they're followed throughout their hospital
9 course by the poison center by telephone, and that leads
10 to reporting on QA and QC. Now, 49 of these 60 poison
11 centers in the United States currently participate in
12 the RADARS System, and if you take their coverage areas,
13 their jurisdictions, if you will, that's 240 million or
14 almost 85 percent of the U.S. population.

15 One nice thing about poison centers is you
16 really get 100 percent reporting rate every quarter
17 because we can bug them until they do it.

18 Now, an exposure is defined as an individual
19 taking a drug leading to a call to the poison center,
20 some type of event. Often, there are medical symptoms
21 and signs. Sometimes it is I took an extra dose of
22 medication. Will that lead to an adverse event? For

1 just the opioids and RADARS' participating poison
2 centers, there were over 42,000 exposures reported in
3 2009.

4 So, we have quite a bit of baseline data on
5 these medications. This shows the reported intentional
6 exposures using the denominator of population. We also
7 can use the denominator of individuals filling a
8 prescription for the drug, but for simplicity's sake,
9 I'm showing this as the population denominator.

10 You can see in the purple line, which is
11 immediate-release oxycodone, that there has been a
12 relentless increase in the amount of just a single
13 entity immediate-release oxycodone over the past seven
14 years. The orange line is OxyContin. OxyContin has
15 been more stable, but has a slight increase in 2008 and
16 2009. the yellow line is generic extended-release
17 oxycodone, which was introduced in 2004, and has
18 subsequently been largely withdrawn from the market.
19 So, it came, was detected by the Poison Center Program,
20 but then has gone back down as the drug was decreased.

21 If we focus just on OxyContin in this slide,
22 we have the Poison Center data just for OxyContin with

1 the rate of intentional exposures again. The orange
2 line is the combination actually of OxyContin and the ER
3 oxycodone. The light blue lines are the 95 percent
4 confidence intervals around that number, and then, as
5 you'll see, and these data, I should point out, go
6 through June of 2010.

7 So, in RADARS, we report out our data three
8 months after the close of each quarter. So, we have
9 data through June. That's all real data up to that
10 dotted line. And then after the dotted line are the
11 potential effects of the introduction of a new
12 formulation of OxyContin. And, as you can see, the
13 hypothesis would be that it could continue unchanged.
14 In theory, it could even increase, but, for some reason,
15 the new formulation was more attractive and used more.
16 Or it could decrease, as shown by the orange triangles.

17 We're also going to look at the case fatality
18 rate for OxyContin. This slide is just a sample to
19 compare OxyContin to methadone. Methadone was chosen
20 because it has the highest case fatality rate in the
21 RADARS' Poison Center Program. I've broken the ages
22 into greater than 12 and less than 12-years-of-age, but

1 we get the patient's age in each case. So, we can
2 analyze this by any age group that you would like.

3 For methadone, if you take the younger
4 patients, you can see that there are still some deaths,
5 but over the period of 2003 to 2009, there were only 7,
6 although, in my world, 7 is a lot. And then as people
7 get older, you can see the rate goes up to 241 deaths.
8 So, really 1.5 percent of cases coming to a poison
9 center involving methadone end up as a fatality.

10 For OxyContin, the rates are lower. I'd say
11 there's relatively high, but lower than methadone. For
12 greater than 12, it was .58 percent.

13 If we plot the trends of these over the years,
14 this shows methadone, fentanyl, OxyContin, and
15 hydrocodone. You can see that fentanyl and methadone
16 group in the top two lines and OxyContin and hydrocodone
17 in the bottom two lines. And the baseline data here is
18 relatively stable, which will help us see a difference
19 if one occurs after the introduction of OxyContin.

20 To summarize that study, what we'll be looking
21 at will the incidence rate, the first slides I showed,
22 change after the introduction of the new formulation,

1 and will the case fatality rate change after the
2 introduction of the new OxyContin?

3 These calls come from the general population.
4 In fact, all poison centers have to solicit calls from
5 the entire population of their service area. It's an
6 observational time series. And the primary outcome will
7 be the case fatality rate, but also the incidence rate,
8 as I mentioned. We have seven years of baseline data,
9 and we think that we will see an effect in six to nine
10 months if there is an effect.

11 I mentioned that a case is an intentional
12 exposure, and an incidence rate will be calculated
13 simply by taking the cases per quarter for a specific
14 medication and dividing it by the population that was
15 actually covered by the poison centers covering that.
16 That's the 85 percent I was describing earlier.

17 Case fatality rate is a measure of toxicity,
18 and this is exposures resulting in death divided by the
19 total exposures. The idea is that a change in toxicity
20 of OxyContin could result in a decreased case fatality
21 rate. We can use any opioid comparator that you would
22 like because we collect this information on all of the

1 opioid medications.

2 For our analytic approach, the case fatality
3 rate is an interrupted time series. We have to realize
4 that event rates are relatively low, and, so, the data
5 will be analyzed using a Poisson distribution.

6 The time series data tend to be auto
7 correlated. So, data will be modeled to allow the
8 current inferences. Separate trend lines will be fit
9 before and after the formulation change. All of this is
10 accommodated by using a generalized linear mixed model.

11 The main limitation to poison center data is
12 that calling a poison center is not mandatory. It's a
13 voluntary act by someone or their friends or family who
14 feel a need after an exposure to call the poison center.
15 However, it's a large system, and it seems unlikely that
16 systematic changes will occur across all 49 centers
17 simultaneously, and our long track record of baseline
18 data will help us show that.

19 The main strength is that it has large
20 national coverage of the general population, and we have
21 consistent data collection. All centers use the same
22 data fields, as I mentioned, but RADARS has a specific

1 change unique to RADARS.

2 If you think about NPDS, the National Poison
3 Data System of the AAPCC, American Association of Poison
4 Control Centers, all these centers participate in both
5 systems. In fact, the data feed for RADARS is identical
6 to NPDS. The difference is that we collect more fields,
7 and, in particular, we collect what's called the case
8 notes for each case. These are notes that the
9 specialist fills out during the case. We use that
10 information to check fields like product coding and
11 route of administration to make sure that that data is
12 accurate and internally valid.

13 As I mentioned, the data are available within
14 three months of the close of each quarter, and another
15 advantage that's my particular favorite is that cases
16 involving children can be analyzed separately to see if
17 there's any unintended effects of the introduction.

18 DR. COPLAN: Thank you.

19 So, the first two studies addressed the
20 outcomes of overdose and death. The third study, now
21 we'll move on to studies that will address the first
22 three outcomes. The next study will address routes of

1 abuse and usage and demand. And Ms. Theresa Cassidy
2 from Inflexxion, director of Epidemiology at Inflexxion
3 will present the next study.

4 Thank you, Theresa.

5 **OxyContin Abuse Among Entrants to Substance Abuse**
6 **Treatment Programs**

7 MS. CASSIDY: Thank you, Dr. Coplan.

8 Good afternoon. I am Theresa Cassidy,
9 director of Epidemiology at Inflexxion. Inflexxion is a
10 private public health research and technology company
11 with expertise in substance abuse research. We provide
12 risk management and post-marketing surveillance services
13 to pharmaceutical companies through the NAVIPRO System.
14 I have no personal financial interest in the outcome of
15 this meeting, but I have been paid by Purdue for my
16 time.

17 We will be conducting the study of abuse of
18 the reformulated OxyContin among adults entering
19 substance abuse treatment programs. Through NAVIPPRO's
20 ASI-MV Connect data, we have over three years of
21 baseline on abuse of OxyContin. This graph shows
22 baseline route of administration data for three drugs

1 from the ASI-MV Connect Treatment Center Network since
2 2007. For OxyContin, shown farthest to the left, a
3 variety of routes of administration are reported by
4 adults in treatment, with the most frequently being
5 snorting at 58 percent, followed by oral administration,
6 and then injection.

7 In contrast, injection is reported most
8 frequently from morphine extended release products,
9 while snorting is a little bit lower in frequency. And
10 the most common route of abuse reported for hydrocodone
11 is oral administration at 92 percent.

12 Monitoring changes in the route of
13 administration profile will be a key element to
14 evaluating the question of tamper-resistance for the
15 reformulated OxyContin. As observed from the baseline
16 data just shown, specific route of administration
17 profiles exist for different prescription opioid
18 products.

19 From our data, we have observed that these
20 profiles can be used to characterize a drug's pattern of
21 abuse because the profiles are distinct, they can be
22 differentiated from one product to another, and they

1 tend to be stable over time.

2 For example, these baseline data show the
3 different routes of administration reported for
4 OxyContin by adults entering substance abuse treatment
5 are generally consistent and have been stable since
6 2007.

7 The objective of our study is to assess both
8 the route and frequency of abuse for the reformulated
9 OxyContin pre and post launch in comparison to other
10 prescription opioids. The study population includes
11 adults entering treatment programs from a defined
12 network of centers using data from ASI-MV Connect. This
13 observational surveillance study will measure recent or
14 past 30-day abuse and specific routes of administration
15 reported by abusers of OxyContin and other opioid
16 products.

17 The ASI-MV Connect has more than three years
18 of baseline data to use for comparison, and we
19 anticipate being able to observe a change within six to
20 nine months after the full introduction of the
21 reformulated OxyContin.

22 To provide a little background on our data

1 source, the ASI-MV Connect collects information in near
2 real-time from a network of about 500 treatment programs
3 across the United States located in 36 states. The data
4 are collected using a computerized interview, which is a
5 standardized and validated instrument required during
6 clinical intake to treatment. Individuals identified
7 drugs that they've abused through pictures, drug names,
8 and street names, and the data are self-reported and
9 identified so that they are HIPAA-compliant.

10 This study will use statistical modeling
11 approaches that apply regression analysis to assess both
12 the frequency of abuse and the routes of administration
13 over time. We will compare the difference in the
14 proportion of patients reporting past 30 day abuse of
15 OxyContin pre and post reformulation. We will also
16 compare the difference in the continued rate of abuse by
17 measuring the number of days that a patient has reported
18 abuse within the past 30 days prior to treatment.

19 The modeling approach will take into
20 consideration adjustment for factors such as
21 prescription volume and geographic location. For route
22 of administration, we will compare the differences in

1 the proportion of patients reporting abuse through
2 different routes with specific breakdowns for the oral
3 category that includes swallowing whole, chewing, and
4 other oral routes of administration.

5 One limitation to the study is that the sample
6 is now representative of all those entering substance
7 abuse treatment nationally, but rather are collected
8 from the 500 centers located in 36 different states.
9 Also, the ASI-MV Connect Network does not necessarily
10 collect data from individuals who do not seek treatment.

11 The study does, however, exhibit strengths,
12 and these include the use of consistent measurements
13 over time that allow for reliable detection of
14 differences in the route of administration profile for
15 the reformulated OxyContin, and this among a sentinel
16 population that is at high risk of abuse for
17 prescription opioids.

18 Additionally, the online data collection
19 methodology that we use allows for timely analysis and
20 for prospective outcome monitoring with a high level of
21 specificity.

22 DR. COPLAN: Thank you, Ms. Cassidy.

1 The next study, we'll use surveys, in
2 particular, the NSDUH survey, and we'll be looking at
3 routes of abuse, usage and demand, and addiction in the
4 study, and it'll be presented by Dr. Howard Chilcoat,
5 director of Epidemiology at Purdue.

6 **Using Surveys to Assess the Impact of a New Formulation**
7 **of OxyContin**

8 DR. CHILCOAT: Thank you, Dr. Coplan.

9 Data from national surveys on drug use will be
10 a valuable tool to help us understand the impact of the
11 reformulation of OxyContin on non-medical use in the
12 U.S. population. One survey that you've seen presented
13 earlier in several presentations is the National Survey
14 on Drug Use and Health, or NSDUH, which is often used to
15 examine trends in drug use. We can use NSDUH data to
16 provide baseline data on non-medical OxyContin use.

17 As shown on this slide, these NSDUH data show
18 the percentage of the U.S. population that used
19 OxyContin non-medically from 2004 to 2009. There's been
20 a slight increase in non-medical use of OxyContin during
21 this period. In particular, the recently-released 2009
22 data show an uptick to 0.7 percent from levels of around

1 .5 percent from 2004 to 2006. We'll have to wait for
2 the 2010 data become available to see if the increase in
3 2009 represents a trend. Then we will look to see what
4 happens to this trend after the introduction of the
5 reformulation.

6 Our plan is to use data from NSDUH and three
7 other national cross-sectional surveys to compare trends
8 in the prevalence of non-medical use of OxyContin and
9 other prescription opioids. These surveys are measured
10 in a systematic way year by year and cover the vast
11 majority of the population. Because these surveys have
12 assessed non-medical OxyContin use for up to six years
13 prior to the introduction of the reformulation, they
14 provide a useful baseline.

15 However, due to the time needed to collect the
16 data each year and prepare datasets for public use, it
17 will be at least two years before we see an effect from
18 these studies.

19 We plan to use data from four different
20 national surveys, as outlined on this slide. These
21 surveys include the NSDUH, as well as the Monitoring the
22 Future Study, Partnership Attitude Tracking Survey, and

1 the RADAR System College Survey.

2 As you can see on this table, the studies have
3 different age ranges and sample sizes. The MTF, PATS,
4 and RADARS enroll school-based samples ranging from
5 middle school to college. In the interest of time
6 today, I will focus on our strategy for using NSDUH data
7 because it covers the broadest scope of the U.S.
8 population and has more extensive measures of OxyContin
9 than other surveys.

10 The NSDUH started in 1971, and has been
11 conducted annually since 1990 by the Substance Abuse and
12 Mental Health Services Administration. It interviews
13 over 60,000 respondents each year, and the survey
14 methods have not changed since 2002, allowing trend
15 comparisons for years since then. The NSDUH has
16 collected data specific to OxyContin since 2004.

17 Our strategy for using NSDUH data will be to
18 examine trends for several outcomes of non-medical use
19 of OxyContin and other prescription opioids. We will
20 look at the period prevalence, frequency of use, recency
21 of use, and the presence of DSM-IV dependence diagnosis.
22 We will depict prevalence used trends graphically and

1 then we will compare trends across the time periods
2 before and after the introduction of the reformulation.

3 The most commonly used measure in surveys such
4 as NSDUH is period prevalence, which captures the
5 percentage of the U.S. population who use a drug in a
6 specified timeframe such as in the year prior to survey,
7 as I showed earlier.

8 The orange line represents the population of
9 past year OxyContin users. However, it combines all
10 users from experimenters who have used the drug just
11 once orally all the way to daily injectors who are
12 addicted. And as Dr. Coplan described earlier, it's
13 possible that the reformulation of OxyContin might have
14 varying effects on abuse and different populations,
15 depending on route of administration and stage of use.

16 To get a better understanding of the different
17 populations this orange line represents, we have divided
18 OxyContin users by frequency of use. Frequency of use
19 is associated with route of administration and stage of
20 drug use, and we expect that the formulation would have
21 a greater impact on more versus less-frequent users.

22 The blue line shows the trends for low

1 frequency use, defined here as less than once a month.
2 And the yellow line shows a trend for high frequency
3 users, those who use monthly or more on average. By
4 disaggregating by frequency of use, we begin to see
5 different trends emerge. Existing data through 2008
6 indicates that the overall increase in the overall
7 prevalence is accounted for by increases in frequent
8 use, whereas low frequency uses remain relatively
9 stable.

10 We'll extend this analysis by using future
11 NSDUH data. We will start by comparing trends in any
12 OxyContin use before and after the introduction of the
13 reformulation. The dotted lines on the right-hand side
14 of the slide represent hypothesized changes following
15 the introduction of the reformulation. We'll examine
16 whether there's an overall decrease in non-medical use,
17 and then explore whether the changes are specific to
18 frequent users or occasional users.

19 I've highlighted frequency of use in the
20 presentation, but we will look at several other
21 indicators of abuse. We will explore whether the impact
22 of the reformulation is greater for persistent versus

1 recent onset use, as well as by history of prior other
2 drugs. We will see whether the occurrence of DSM-IV
3 dependence changes among those using OxyContin non-
4 medically, and we can even possibly explore whether
5 there's a switch to heroin once the reformulation is
6 available by assessing the occurrence of heroin use
7 among former OxyContin users.

8 In this way, we can gain greater insight into
9 the pathways through which the reformulation might
10 affect abuse at the level of the population. We
11 understand it is possible that the changes that we
12 observe in OxyContin use after the introduction of the
13 reformulation could be caused by overall trends in non-
14 medical use of prescription opioids that are unrelated
15 to OxyContin. It will be necessary for us to do a
16 parallel set of analyses for all prescription opioids to
17 see if the changes are specific to OxyContin.

18 As we looked at all the national surveys, we
19 noted that while they have a number of strengths that
20 will assist our works, they also have some limitations.

21 The limitations of large-scale survey data are
22 well-known. It's been discussed today. Retrospective

1 self reports are subject to underreporting and under
2 reliability.

3 However, because these surveys use consistent
4 methods each year, it is unlikely that the changes in
5 trends would be due to differential underreporting over
6 time. With the exception of the RADARS College Survey,
7 the surveys did not measure different routes of
8 administration of OxyContin. However, the available
9 data will allow us to look at frequency of use, as well
10 as other indicators of abuse that might be related to
11 route of administration.

12 In addition, the surveys did not capture
13 certain populations. For instance, it's been discussed
14 earlier the NSDUH doesn't include those in institutional
15 settings. The school-based surveys don't include
16 students who have dropped out or not attending school.
17 But we don't expect this limitation to affect trends.

18 Among strengths, these surveys capture
19 patterns of non-medical use in the general population
20 rather than specialized samples, such as those entering
21 treatment. Only about 10 percent of those with opioid
22 dependence ever receive treatment, and, so, we need to

1 go beyond this group.

2 The surveys also ask OxyContin-specific
3 questions, which will be vital for our work. It will
4 give us a well-established baseline upon which to
5 compare trends following the introduction of the
6 reformulation. So, until the data from the new
7 formulation come in, we will analyze existing data to
8 better understand how OxyContin and other opioids are
9 used and develop a baseline against which we will
10 compare findings found in the introduction of the
11 reformulation.

12 So, although it may take awhile, we believe
13 that the data from national surveys will significantly
14 contribute to our understanding of the impact of a
15 formulation designed to make it more difficult to
16 manipulate OxyContin for the purpose of abuse.

17 Thank you.

18 DR. COPLAN: Thank you, Dr. Chilcoat. The
19 next study of law enforcement in the RADARS System,
20 it'll be measuring demand for purposes of abuse, and
21 will be presented by Professor Rick Dart.

22 **Law Enforcement Events in the Drug Diversion Program of**

RADARS System

DR. DART: Thank you.

The Drug Diversion System in RADARS is a network of about 300 reporters in 50 states that are either in local law enforcement agencies or in some statewide taskforces that report each quarter about the new cases in their area. So, for new case of diversion, the investigator in that area submits a report using a standard report tool into the database, and that's reported out quarterly in terms of incidence rates for that jurisdictional area.

This program is run by the Center for Drug and Alcohol Studies from the University of Delaware, and it currently covers 658 of the 3-digit zip codes in the country, and there are about 960 or 70 of those. It's about 68 percent of the total population, and for the first 8 years, reported over 77,000 events of diversion.

So, this system has a lot of baseline data, as well. This is the same structure as my previous slide which shows the incidence rate on the right per 100,000 population. The purple line is immediate-release oxycodone, the orange line is OxyContin, and the yellow

1 is the generic extended-release form of oxycodone.

2 As you can see, it's a very similar trend in
3 both of the RADARS' programs. We've experienced
4 dramatic increases in immediate-release oxycodone over
5 the last few years, and some increase in OxyContin, as
6 well. These in general have been quite related to the
7 number of people filling a prescription for those
8 medications.

9 What we will study here is the question will
10 diversion of OxyContin and comparators change after the
11 introduction of the new formulation? The population is
12 unique; it's drug dealers and diverters. It's
13 standardized surveillance from a long-established
14 network of centers, and the outcome really is the number
15 of new drug diversion events in that jurisdiction each
16 quarter. We have eight years of baseline data, and we
17 think we will see an effect in the system in six to nine
18 months.

19 Just to clarify a little bit about what a case
20 is, specifically, it involves a new written report
21 investigated during the prior three months. This has to
22 be documented in the legal records and their arrest

1 records. And this is based on attempt or actual
2 diversion based on legal prescriptions, physician or
3 pharmacy reports of prescriptions, empty prescription
4 bottles, or actual drugs seized, such as in a buy.

5 The incidence rate for drug diversion events
6 is just simply the number of cases reported divided by
7 the population for that jurisdiction, and we add all
8 those together to get the total. This system also
9 collects street price. I hadn't planned on including
10 that in the presentation, but if there's questions, I
11 can answer them during the Q and A.

12 For our analytical approach, this is very
13 similar to what I presented for poison centers, an
14 interrupted time series with low rates. We're going to
15 have to model that to allow correct inferences and we're
16 going to include covariates, such as local prescription
17 availability and geographic location.

18 This shows a slide of reported diversion
19 events from 2004. The data through mid-2010 is actual
20 data from the system, showing OxyContin, and it's 95
21 percent confidence intervals. The orange lines to the
22 right of the dotted line labeled "New Formulation" are

1 the potential outcomes here. And, as I described
2 before, we'll be looking for either no change or a
3 substantial decrease in the diversion of OxyContin.

4 As I mentioned, we can also look for a change
5 in the price on the street of OxyContin. If demand
6 decreases, we should see a decrease in the price.

7 The primary limitation of law enforcement data
8 is potential for reporting bias, and intensity of
9 enforcement focus can vary somewhat. These
10 professionals are responding to the needs of their
11 community, and sometimes prescription drug abuse is
12 primary, and sometimes it isn't. However, you can see
13 from the baseline that we have long-term data over eight
14 years, and we don't think that that will change
15 substantially, with over 300 investigators
16 simultaneously.

17 Another point I want to make is that the data
18 don't represent pain patients, and a previous speaker
19 mentioned this, but it's really important to understand
20 that we may think they're pain patients, but, in
21 reality, most of these are not pain patients. They're
22 dealers who are making a profit, entrepreneurs, if you

1 will, trying to make a profit.

2 The strength of our RADARS System is that we
3 create a mosaic by reporting from multiple stakeholders
4 and perspectives on the same phenomenon, and a positive
5 strength of the Drug Diversion System is that the
6 product is available usually for accurate identification
7 because they seized it in the arrest. And, as with our
8 other systems, the data available within three months of
9 the close.

10 **Doctor Shopping for OxyContin as Measured by**
11 **Prescription Monitoring Programs**

12 DR. COPLAN: The next study is a measure of
13 Doctor Shopping Prescription Monitoring Programs and
14 this is a measure of usage and demand.

15 Doctor shopping occurs when individuals visit
16 numerous physicians to obtain multiple prescriptions.
17 The excess drug can be abused or diverted. Prescription
18 Monitoring Programs were developed to track abuse and
19 diversion of prescription drugs at a state level.
20 Thirty-four states have operational PMPs. Delaware has
21 recently been added. The slide by Dr. Dormitzer was
22 correct. To date, two state PMPs have agreed to share

1 data for analyses, Ohio and Connecticut. We've also
2 been in discussions with other PMPs, such as
3 Massachusetts, Maine, North Carolina, and Utah to
4 participate in sharing data for an analysis.

5 The objective of the study is to assess
6 whether the number of people who doctor shop for
7 OxyContin decreases with the new formulation. The study
8 population of people receiving opioid prescriptions in
9 the states covered by the PMPs. The design is an open
10 cohort study comparing changes in doctor shopping for
11 OxyContin and compared to opioids using data collected
12 by the PMPs. And the outcome measure for the studies,
13 the number of individuals who doctor shop.

14 The baseline data is approximately two to
15 three years. It has been collected in the existing
16 PMPs, and we predict a time to see an effect of
17 approximately 12 months.

18 There are two phases of the study. The first
19 phase of the study will develop and validate an
20 algorithm to measure doctor shopping by combining the
21 data elements in the PMP databases to measure doctor
22 shopping. And the second phase in the analysis will

1 analyze changes in rates of doctor shopping using the
2 identified data.

3 The data elements that are available to detect
4 doctor shopping in the database are the number of
5 prescribers per time and the number of pharmacies per
6 time. These have been used in the published literature,
7 for example, by Dr. Ned Katz, to look at whether there's
8 a change in the rate of measures of doctor shopping over
9 time.

10 Other researchers, primarily in Europe, in
11 France, have used overlapping dispensing periods of
12 repeated prescriptions or fills for opioids as a measure
13 of doctor shopping.

14 The measure of quantity and dose of
15 prescriptions can sometimes be indicative of a doctor
16 shopping. In addition, cash payments can be indicative
17 because people who are doctor shopping tend not to use
18 insurance since the insurance can pick up the multiple
19 prescriptions. In addition, if the patient is receiving
20 benzodiazepine prescriptions, that also can be
21 indicative and would also be captured by the PMP. We
22 will calculate a rate of doctor shopping, which is the

1 number of doctor shoppers divided by either the number
2 of prescriptions or the Census population in that area.

3 One limitation of the study is that there is
4 no gold standard to measure doctor shopping. This could
5 lead to a high false positive rate of doctor shoppers.
6 However, the false positive rate should be relatively
7 consistent over time when measuring trends.

8 And also, this could be addressed by varying
9 the sensitivity and specificity of the doctor shopping
10 measures, as was indicated by Dr. Paulozzi in his
11 presentation and seeing how that changes the trends.

12 In addition, the study is somewhat limited by
13 the geographic coverage of the PMPs who participate in
14 the study. One strength of the study is that it
15 provides an assessment of the desirability of OxyContin
16 for purposes of abuse, and it complements a study of
17 substance abuse treatment centers because the PMP study
18 population is not limited to those who seek treatment.

19 The next study will look at Internet
20 discussions, and this is a measure of routes of abuse
21 and usage and demand.

22 **Internet Discussion About Reformulated OxyContin Abuse**

1 MS. CASSIDY: Thank you.

2 This study also uses data from the NAVIPPRO
3 System to study Internet discussion about abuse of the
4 reformulated OxyContin.

5 A number of Web Sites exist that support
6 active discussion forums solely devoted to recreational
7 illicit drug use. Drug users who frequent these Web
8 Sites freely offer their ideas and beliefs, discuss
9 trends and preferences, and they offer information and
10 warnings about prescription medications. Many of them
11 provide suggestions and instructions in the form of
12 recipes for the physical and chemical extraction of
13 active ingredients. We can examine these conversations
14 on Web Sites for a discussion related to a number of
15 different topics, including routes of administration for
16 specific products, product comparisons, pill
17 identification, and methods for obtaining drugs for
18 illicit use.

19 Monitoring these Internet discussions allows
20 review of unfiltered opinions on various prescription
21 drugs among a sentinel population of abusers. These
22 discussions provide early indications on whether abusers

1 attempt to tamper with a product for abuse by alternate
2 routes of administration. And, more importantly, these
3 discussions are available for wider dissemination among
4 non-participants who view the information, but do not
5 actively participate in these discussions.

6 The objective of this study is to assess
7 differences in the pattern of Internet discussion among
8 drug abusers regarding the new formulation of OxyContin.
9 The population for this study are drug abusers on the
10 Internet and the study uses an observational
11 surveillance approach. Using NAVIPPRO Internet
12 Monitoring Data from a number of drug discussion Web
13 Sites, we will examine the proportion of discussion
14 related to conversations about tampering, routes of
15 administration, and overall sentiment by drug abusers
16 regarding the new formulation.

17 This approach is currently being used by a
18 number of companies as part of their FDA post-marketing
19 surveillance requirements. We have been monitoring
20 Internet discussion for the original OxyContin, and have
21 over three years of baseline data. Given the nature of
22 this type of surveillance, the data are available in a

1 quick timeframe, and we estimate that it would take
2 approximately three to six months after the introduction
3 of the new formulation to determine an effect of whether
4 there is a change among abusers in the nature of their
5 discussion in their interest in abusing this drug.

6 Although, it is not possible to quantify all
7 of the Internet discussion regarding the new
8 formulation, we are able to gain an understanding of the
9 types and the level of conversation occurring among drug
10 abusers within a stable community of individuals who are
11 on these selected Web Sites. This study is designed to
12 characterize differences in online discussion between
13 the old and the new formulation of OxyContin by
14 quantifying the proportion of posts, threads, and unique
15 authors that contribute to the conversation about the
16 drug.

17 One example of quantifying the level of
18 discussion is to calculate the proportion of posts
19 pertaining to a particular product over the total number
20 of posts on a selected Web Site. We can use this
21 approach to evaluate the number of individuals that
22 contribute to the conversation and to quantify the level

1 of discussion for specific topics.

2 To characterize Internet discussion by topic
3 area, we will obtain and review a random sample of drug-
4 specific posts. The posts are then reviewed and rated
5 by research staff using standardized coding procedures
6 to assess the sentiment of the message, including
7 whether the author endorses, discourages, or has mixed
8 comments about abusing the drug.

9 For example, if an author would post that they
10 enjoyed getting high from OxyContin, this would be coded
11 as endorsing the product for abuse. But, alternatively,
12 if an individual references being addicted, which is
13 typically referenced in a negative connotation, or warns
14 against using OxyContin, this would coded as
15 discouraging the product for abuse.

16 To ensure consistency between coders and over
17 time, inter-rater reliability is assessed using blinded
18 co-samples. And these methods are used to code posts by
19 topic area including the routes of administration and
20 recipes for tampering with the drug.

21 These baseline data shows sentiment in
22 Internet discussion for three categories from a sample

1 of posts for the original OxyContin and hydrocodone
2 products since 2007. The data indicate that OxyContin,
3 shown here in the orange bars, is more frequently
4 discussed in an endorsing manner among drug abusers
5 online at 38 percent of the sample of posts. In
6 contrast, sentiment towards abuse of hydrocodone
7 products shown here in the blue bars is ambivalent, with
8 an equal percentage of posts endorsing and both
9 discouraging the product.

10 We have observed some early Internet
11 discussion on the reformulation, and, in general, the
12 early discussion indicates dislike and frustration with
13 the reformulation by abusers. The question was asked
14 here by the committee earlier if we are aware of any
15 information about the street price of the drug, and we
16 have seen some evidence of increases in the street price
17 of the original OxyContin, as shown in this example.
18 We've also seen intention by abusers to switch to other
19 opioid products preferred for abuse.

20 Like any data source, there are certain
21 limitations to the study of Internet discussion, and the
22 nature and size of the Internet make it impossible to

1 quantify and report on all discussions specific to the
2 new formulation. In addition, the extent to which these
3 data may relate to increase or decreases in population-
4 based trends of abuse is uncertain. Other factors, such
5 as the availability of a drug in any particular location
6 may also influence what is being abused there, and then
7 subsequently discussed online.

8 Study of Internet discussions, however, have a
9 number of strengths. Analyses from the Internet
10 discussion can act as a rapid sentinel surveillance
11 system among sentinel population of abusers who are
12 motivated to tamper with the product for abuse.
13 Monitoring these discussions over time allows to detect
14 changes in how, why, who, and sometimes even where
15 diversion in formulation tampering can occur. Another
16 strength is that we have more than three years of
17 baseline data to use as a comparison and that the data
18 collection and analytic procedures that we are using are
19 consistent over time to allow for changing patterns.

20 DR. COPLAN: Thank you.

21 The next study is abuser cohort in Kentucky.
22 This study will follow-up individuals over time and will

1 assess the measures of routes of abuse, demand for
2 reasons of abuse, and also the outcome measure of
3 addiction.

4 Professor Carl Leukefeld from the University
5 of Kentucky will present.

6 **Changes in Abuse Patterns in a Cohort of People Abusing**
7 **OxyContin in Rural Kentucky**

8 MR. LEUKEFELD: Thank you.

9 I'd like to start by saying I have no personal
10 financial interest in the outcome of this meeting. I
11 have been paid by Purdue for my time, and I have no
12 interest in the outcome of the study.

13 Our research team has been studying drug abuse
14 for prescription drug abuse as well as illegal drug
15 abuse in rural Kentucky for several years. As a result,
16 we have a good understanding of the baseline of
17 OxyContin abuse in this population.

18 Let me first give you some background on this
19 region and the cohort, and then I'll discuss the study's
20 objectives and methods.

21 Research indicates that prescription opioid
22 abuse and dependence is more prevalent in some rural

1 areas, thus, we believe we have been working with a
2 sentinel population for this type of research.

3 In addition, government and media reports have
4 pronounced that prescription opioid misuse is at
5 epidemic levels in the Appalachian regions of Kentucky,
6 Virginia, and West Virginia, where it is thought that
7 long and labor-intensive work, such as mining and
8 logging, has helped to create what has been called a
9 pain culture. This supposition is supported by 2004 to
10 2008 national data.

11 In our own 2007 study, more than 40 percent of
12 those indicating past 30-day prescription opioid abuse
13 that also injected during their lifetime, and our cohort
14 every OxyContin abuser reported injecting OxyContin,
15 which was surprising, and this is in the same study,
16 same county that we focused our current study on. In
17 contrast, significant and a number of injectors who had
18 said they had Hepatitis C was significantly greater than
19 those who did not inject.

20 Another study described the routes of
21 administration for prescription opioids. We have
22 previously studied these 101 opioid abusers in Perry

1 County. What we found was a high rate of snorting
2 behavior across all drugs, and a high rate of injection
3 behavior with OxyContin specifically. With this in
4 mind, I will now move on to the overview of the study we
5 are about to undertake.

6 The objective of our study is to describe
7 changes in use and abuse patterns of OxyContin following
8 the introduction of the reformulation. We will
9 interview and follow 200 OxyContin abusers to examiner
10 self-reported changes in routes of administration and
11 preparation methods.

12 Let me say something about Perry County,
13 Kentucky. It has been popularized in the media. There
14 are about 30,000 folks who live there. The main city is
15 Hazard, of about 5,000 people, with a population that is
16 30 percent below the poverty line, and there are limited
17 economic opportunities there after the coal mining
18 industry collapsed. We're going to collect both
19 qualitative and quantitative data. We'll recruit people
20 who have been abusing OxyContin from a variety of
21 sources. More than half will likely have been
22 participants in an ongoing study of a current study of

1 prescription opioid abusers in Perry County. We expect
2 baseline enrollment to be completed by early next year.
3 We'll also use qualitative extensive face-to-face
4 interviews with 15 randomly-selected participants about
5 the impact of the new formulation in their own drug use,
6 about the patterns of their drug use, and about what
7 drug use means to their family, friends, as well as
8 others in the community. The follow-up structured
9 interviews will be about three to six months after the
10 baseline to assess any changes.

11 These interviews will be conducted by a
12 trained interviewer, and will be quite detailed to gain
13 a picture of how these people abuse drugs.

14 Our structured interviews will assess what you
15 see here across and within individuals, preparation,
16 administration, abuse, opioid abuse. We'll use the
17 addiction severity measures to look at symptoms and look
18 at symptoms of abuse and dependence, rates at which
19 people change their use of OxyContin, other prescription
20 opioids, and other drugs after the reformulation.

21 Our particular interest will be determining
22 the extent to which OxyContin abusers switched to other

1 opioids, such as IR oxycodone methadone tablets or
2 heroin. As with any study, this one has certain
3 limitations, and our findings will need to be considered
4 in light of these, including the single geographic area,
5 some limited generalized ability, reliance on self-
6 reports.

7 Along with these limitations are: the
8 extensive qualitative and quantitative data will provide
9 an opportunity to conduct exploratory data analysis, as
10 well as to apply more complex statistical approaches.
11 We believe we will be able to examine changes in the
12 abuse of other opioids as a sentinel population. Our
13 follow-up with individuals who are abusing OxyContin
14 when the reformulation is introduced provides a way to
15 directly assess changes in abuse behavior.

16 Finally, this study represents an
17 extraordinarily opportunity for us to examine the abuse
18 of opioids. We can now hypothesize at a reformulation
19 an abused drug might make a measurable impact in drug
20 abuse behaviors which we have not been able to do in our
21 studies for the last 20 years.

22 Thank you.

1 DR. COPLAN: Thank you, Professor Leukefeld.

2 **Summary and Conclusions**

3 Taken together, the eight studies are designed
4 to make the most of the existing data sources to piece
5 together a clear picture of changes in patterns of
6 abuse. The mosaic of studies that we've assembled to
7 address FDA's request help to disaggregate the drivers
8 of abuse and its outcomes. We have a particular focus
9 on studies routes of administration to assess the impact
10 of the new formulation, and we've attempted to
11 incorporate wherever possible different geographies and
12 populations. The results will inform us and FDA of the
13 impact, if any, of the reformulation in the real world.

14 Interpretation of the eight studies will be
15 focused on answering the five key questions that we
16 introduced earlier. There are one or two studies that
17 address each question. Our goal is to describe and
18 estimate effects rather than test formal, statistical
19 hypothesis. We'll be looking for substantial effect
20 that is sustained and consistent across the studies.

21 The data collection has already begun within
22 most of the data sources, and it's estimated to take

1 between 6 to 9 months and 24 months to see an effect.
2 These timeframes are our best guess. We will remain
3 diligent in continuing to monitor the effects in case a
4 way to circumvent the new formulation is developed after
5 the two-year horizon, or if additional cases are
6 required for study precision and power, particularly in
7 the Kaiser study.

8 The estimated time to see an effect can be
9 used to determine a proposed duration of the studies for
10 a post-licensure commitment. It is anticipated within
11 two years we'll be able to see an effect. However, for
12 select data, it make take two years to become available,
13 such as the NSDUH data, two years after the
14 observational period. Therefore, the proposed
15 observational period is for two years to be initiated,
16 and we have initiated data collection beginning in
17 August 2010. However, the duration may be lengthened if
18 event rates are lower than expected to increase study
19 power.

20 Purdue will submit annual reports to the FDA,
21 and investigators will independently report their
22 results of their studies. The overall interpretation of

1 the results will consist of an internal assessment by
2 Purdue staff and an independent evaluation by the expert
3 panel that Dr. Landau mentioned in the introduction.

4 The Epidemiologic Study Program is designed to
5 address the five outcomes of interest using eight
6 studies, and this mosaic of studies will provide an
7 opportunity to address the impact of the new
8 formulation.

9 In conclusion, the new formulation is expected
10 to reduce injecting, snorting, and smoking routes of
11 administration of OxyContin by impeding the ease of
12 tampering with OxyContin. These are the routes that are
13 associated with more frequent and independent abuse.
14 Multiple studies are required to demonstrate an effect
15 of the new formulation on various populations, stages of
16 abuse, and outcome measures. We've designed eight
17 studies to provide a comprehensive picture of the impact
18 of the new formulation.

19 If the approach of the tamper-deterrent
20 formulation is demonstrated to be effective for
21 OxyContin, the approach may be generalizable to other
22 prescription opioids. Our goal today is to develop the

1 best possible studies to address the questions about the
2 potential impact of the new formulation, and we welcome
3 the input of the panel in designing these studies.

4 Thank you for your attention to this rather
5 long presentation.

6 DR. KIRSCH: Thank you.

7 We will now take a 15-minute break. Committee
8 members, please remember that there should be no
9 discussion of the meeting topic during the break amongst
10 yourselves or with any member of the audience. We will
11 resume at 3:15.

12 (Break.)

13 **Clarifying Questions**

14 DR. KIRSCH: All right, we're going to restart
15 the last part of the session for today. And this is a
16 session, if everyone could take their seats, for
17 clarifying questions to the Sponsor. So, if you have a
18 question, raise your hand, and we will recognize you.

19 Dr. Fletcher?

20 DR. FLETCHER: Thank you. I'd like to
21 congratulate the Sponsor and also FDA for kind of laying
22 out the various databases and the information about

1 prior exposure and information about existing and
2 stability of some of the measures that are proposed
3 going forward prospectively to see changes in, but I
4 wondered if particularly the Sponsors the individual
5 speakers could address the issue of effect size in these
6 various databases and changes.

7 Being a clinician, I'm interested in that, and
8 while FDA's questions don't specifically address effect
9 size, they imply that that's an important aspect of it
10 in our deliberation tomorrow, and I'm wondering, for
11 example, given the baseline levels of data and
12 variability known, what kind of an effect size would be
13 able to be seen in the timeframe of the one to two years
14 for these various programs?

15 I'm particularly interested for Dr. Perrin
16 from the Kaiser Permanente, and, perhaps, Dr. Cassidy
17 and Inflexxion if they could comment about what size of
18 an effect in their measures could they be able to see a
19 difference in based on the information they have
20 already. Just to put in perspective the question about
21 what's clinically important difference for the group
22 tomorrow. So, if anyone would want to address that.

1 DR. COPLAN: Okay. We'll present our three
2 outcomes studies looking at the effect size of each of
3 those. Could we have backup slide 45 for the Kaiser
4 Study, please? Forty-five.

5 And, so, the power calculation for the Kaiser
6 addressed the effect size somewhat. We've tried to
7 avoid setting a mechanistic threshold above which we
8 would call an observed effect a success because we don't
9 really have an evidence base on which to evaluate what
10 would be a priority, what would be a success. So, we've
11 tried to focus more on estimation, and look at the
12 precision to estimate trends or changes.

13 So, in this slide, to detect a 50 percent
14 reduction in the Kaiser Study that Dr. Perrin showed, we
15 would need 4,800 patients for 90 percent power or 3,600
16 patients for 80 percent power, which we're easily able
17 to get, especially if we combined Kaiser Northwest with
18 Kaiser in Southern California and Kaiser in Northern
19 California. They're approximately 6,000 to 7,000
20 patients a year if we combine those 6.6 million roughly
21 from a guess.

22 Dr. Perrin, do you want to add anything?

1 DR. PERRIN: (Off microphone.)

2 DR. COPLAN: Yes, so, to detect an effect size
3 of 75 percent, we would be very well powered. However,
4 below 50 percent, we're really starting to run into an
5 inability to detect effect within one year. So, if it
6 was 40 percent, we probably would be okay with 80
7 percent power, but below that in one year, we wouldn't
8 be able to detect. If we went out two or three years,
9 then, obviously, we would be getting three times that
10 amount of patients, and power would increase.

11 Could we have backup slide 54, please? Fifty-
12 four.

13 So, if we look, another system would be the
14 Poison Control Center, which is another way of measuring
15 outcomes, and, as Professor Dart showed, these are the
16 95 percent confidence intervals around the poison
17 control reports over time for OxyContin, so, it provides
18 an estimate of the precision. The confidence intervals
19 are fairly tight, so, if we saw a 50 percent reduction
20 or a 30 percent reduction, I think that we'd have
21 adequate power to detect that.

22 Professor Dart, did you want to add? I think

1 the power calculation that you did, you had 80 percent
2 power to detect a 24 percent reduction.

3 Theresa, did you want to address the
4 Inflexxion?

5 Did you have anything to add? Sure.

6 DR. DART: I just wanted to mention that I
7 think this question goes both ways because with a high
8 number of events being reported, I think we'll be able
9 to report a change, but whether that's a change that you
10 would recognize as important or the panel or society is
11 one of the issues I have is because we have so many
12 events that if we show a 5 percent decrease, but it's
13 statistically significant, is that really a meaningful
14 change and what that conclusion might be from the
15 advisory committee.

16 DR. FLETCHER: Yes, I greatly appreciate that.
17 It's not your role to necessarily say what are
18 clinically-important differences. I just wanted the
19 committee, because they're the experts here.

20 DR. DART: Right.

21 DR. FLETCHER: To say what the power is to see
22 what kind of a change, and then the deliberation might

1 be informed tomorrow about what the size of these
2 effects are clinically-valid.

3 DR. DART: Sounds good.

4 DR. FLETCHER: So, I completely agree with
5 your conclusion there.

6 DR. COPLAN: Also, could we have back up slide
7 65 to address the Inflexxion System? Sixty-five.

8 So, one of the slides shown by Ms. Cassidy was
9 looking at the baseline data of OxyContin route of
10 administration over time by various rates. We didn't
11 put the Confidence Intervals on this graph because it
12 would be too busy. But they're very small because this
13 is approximately 7,000 patients who are reporting
14 OxyContin abuse. So, again, I think we would have the
15 ability to detect a statistically-significant difference
16 quite easily, but whether that would be clinically-
17 significant would be a different story.

18 DR. FLETCHER: Thank you very much. I think,
19 to me, that's quite helpful for our discussion tomorrow
20 after we've heard all of the presentations. Thanks.

21 DR. KIRSCH: Dr. Walsh?

22 DR. KEETON: My question is for Dr. Landau.

1 So, I'm just asking for a point of clarification. In
2 the early part of your initial presentation, you said
3 that the company is not seeking any claims, and in
4 addition, on the slide, it says that any claims for
5 abuse liability should require substantial evidence to
6 support the claim. So, is it your position that you are
7 never seeking any claims for this new formulation or is
8 it your hope that maybe these studies will yield the
9 substantial data that are needed to support a claim?

10 DR. LANDAU: So, we'd be very happy,
11 obviously, if the studies we proposed were able or
12 provided us a look and we're able to detect a
13 significant change that we in the Agency would agree is
14 meaningful. It's our current position, and not that
15 we're not pursuing a claim, if on the other hand the
16 studies bear out and the Agency believes it's in the
17 best interest of the public health to have this type of
18 information in a package insert, we'd certainly be
19 willing to have the discussion. This is uncharted
20 territory for us, and it's not a path we're ready to
21 pursue at this time.

22 DR. KIRSCH: I'm going to ask the next

1 question, and it's for Dr. Coplan and Dr. Perrin.
2 You've chosen to use the database from Kaiser, and one
3 of the weaknesses of that database, as was pointed out
4 by Dr. Perrin, is that it's an insured population. Two
5 questions related to that.

6 There are many organizations now that have
7 Electronic Health Records similar or identical to the
8 one that's used at Kaiser. Why go to their population
9 which is not representative of most of the United
10 States? And, second, what does one do within that
11 system to pick up patients who are cared for primarily
12 in that system, but who go to other institutions when
13 they have an overdose or have a complication from the
14 treatment that's given to them at Kaiser?

15 DR. PERRIN: I think one of the reasons for
16 the selection of the Kaiser System is because we have 10
17 years of Electronic Medical Records to establish that
18 baseline. A lot of the newer community health centers
19 that we actually work on with other studies do not have
20 a long enough baseline period with Electronic Medical
21 Records. It's a more recent event for them.

22 So, then I think to address your second

1 question, Kaiser does record outside claims. So, if
2 somebody goes to an emergency room that is not Kaiser-
3 run, those are registered into our databases if the
4 health plan is billed. So, we can already see trends in
5 the differences from our initial looks at the data of
6 outside claims that come in, claims of poisonings from
7 outside of the system versus inside of the system. So,
8 that's a key variable that we'll be looking at. If they
9 go outside the system and they ask for Kaiser not to be
10 billed, we will not be able to pick them up.

11 DR. KIRSCH: Dr. Wolfe?

12 DR. WOLFE: I have two questions. You asked
13 the second one, except I'll just add a little piece for
14 Dr. Perrin again. Deaths that occur outside the system,
15 someone is found at home or someone goes to an emergency
16 room or whatever, how do you capture those deaths?

17 DR. PERRIN: We do have death data with codes,
18 Death ICD-10 codes, actually, in our system. So, if
19 their primary care physician was the person who signed
20 the death certificate, they also register that into our-
21 -we have an Internal Death Database.

22 DR. WOLFE: But that, again, assumes it

1 happens within the system. If they die outside the
2 system, go somewhere other, not necessarily getting
3 billed, they just are found dead at home, go there, how
4 do you capture that?

5 DR. PERRIN: We only can capture those deaths
6 through the state death records, which we do check
7 regularly. Now, to be honest, the extent to which the
8 cause of death is easily ascertained on those records is
9 going to be difficult.

10 DR. WOLFE: Right. It's a problem.

11 The other question was for Dr. Dart, and has
12 to do with his slide 53, if you could put that up.

13 My memory is that during the period before the
14 generic prescribing stopped that a significant
15 proportion, 10, 20, 30 percent or more of all
16 prescriptions for oxycodone extended-release were
17 generic, and yet, this slide makes it appear that
18 consistently during this time, the last few dots are
19 probably with almost no prescriptions. That's
20 understandable, but consistently during this time, the
21 rate of intentional exposures per 100,000 population is
22 much less, much lower per 100,000 than with the

1 OxyContin.

2 And the question is: Why is that? I mean,
3 I've heard previously, and it may have nothing to do
4 with this, that on the street or other places, the OC is
5 recognized as OxyContin, and people pick it up, they use
6 it, they sell it, whatever, that might not be true for
7 the generic, but I'm just really curious as to why there
8 are these huge differences between the generic extended-
9 release oxycodone and OxyContin, if you have any ideas
10 about that.

11 DR. DART: I don't have a lot of ideas. I
12 think yours is a reasonable one. Those products were
13 harder to identify. We have a program where we actually
14 orient and educate the poison centers, in other words,
15 new coming products, what they look like and that type
16 of thing, but because it didn't have a clear indicia on
17 it, a lot of times, it's harder to identify those.

18 So, I would say that that's part of it. Part
19 of it was they have somewhat lower sales, although, like
20 you said, they had substantial sales before they
21 started--

22 DR. WOLFE: Yes, I think sometime in the last

1 2 to 3 years, it was 20, 30, 40 percent.

2 DR. DART: Yes, yes. It got up that high, and
3 I think the main reason is that. The other is that Dr.
4 Jim Inciardi, who has passed away, but worked with
5 RADARS, has pointed out many times about the brand
6 loyalty and has published some papers on brand loyalty,
7 and that's a very strong phenomenon among drug abusers.
8 It takes time for them to switch. In fact, he even did
9 some work to show that it takes about three years for
10 them to kind of get the idea that the generic is the
11 same as the branded product and switch to it. So, I
12 think one of the problems there is that they never
13 actually totally became convinced that abusing the
14 generic form was as good as abusing OxyContin itself.

15 DR. WOLFE: Maybe the OC or an OP should be
16 removed from the pill so that it could back to the--

17 DR. KIRSCH: Dr. Flick, next question.

18 MR. WOLFE: That's all. Thank you.

19 DR. COPLAN: Actually, could I just add a
20 quick note to that? We did look at the overdose rates
21 in the Kaiser System generic extended-release oxycodone
22 and branded OxyContin, and during the time period, that

1 actually was in an earlier version on the slide deck.
2 We took it out in order to cut down time. And I don't
3 have it in the backup, but I can show you that at the
4 break. And what is shows is that the overdoes adverse
5 event rate went up slightly at the time of the extended-
6 release oxycodone introduction.

7 DR. WOLFE: The generic?

8 DR. COPLAN: The generic, yes. Yes. I'll
9 show you at the break.

10 DR. KIRSCH: Dr. Flick?

11 DR. FLICK: Just a couple of questions to
12 better understand the databases. On slide 53, with
13 regard to the poison center data, Dr. Dart, these are
14 incidence rates per 100,000.

15 DR. DART: That's right.

16 DR. FLICK: Now, the poison centers, you don't
17 have all poison centers participating.

18 DR. DART: That's correct.

19 DR. FLICK: And poison centers overlap in
20 their coverage areas. Is that right?

21 DR. DART: No. The state has to designate the
22 coverage area for a poison center. So, each one will

1 have a discreet coverage area.

2 DR. FLICK: So, you clearly know the
3 population?

4 DR. DART: That's true.

5 DR. FLICK: Okay. And on slide 83, a similar
6 question with regard to RADARS. Again, these are
7 described as "incidence rates," but based on I think it
8 was ZIP codes or jurisdictions--

9 DR. DART: Right, we match the jurisdiction of
10 the investigator two or three-digit ZIP codes.

11 DR. FLICK: So, do jurisdictions match ZIP
12 codes?

13 DR. DART: They don't match perfectly, so, we
14 have to proportionalize the data sometimes. That's
15 correct.

16 DR. FLICK: Okay. And one brief last
17 question.

18 Ms. Perrin, I think the death certificate data
19 is critical to your results, but you don't sound like
20 you have a very clear and absolute link to death
21 certificate data in your population.

22 DR. PERRIN: We can get access to the national

1 death certificates and the state death certificates. We
2 also have in our own database cause of death for those
3 who have died.

4 DR. FLICK: Well, but certainly there are a
5 significant number of these deaths that occur out of
6 hospital. Those deaths never enter a hospital.

7 DR. PERRIN: Yes.

8 DR. FLICK: And, so, they would only be
9 captured in death certificate data, and I would think
10 that you would not answer by saying we can get access to
11 that. I think you must have access to that, and it must
12 be part of the study.

13 DR. PERRIN: Right, and that makes sense, yes.

14 DR. KIRSCH: Dr. Nelson?

15 DR. NELSON: Thank you. I actually have two
16 questions.

17 Like Rick Dart, I'm intimately involved with a
18 poison center at the New York City Poison Control
19 Center, and we don't contribute. We're 1 of the 20
20 percent of centers that don't actually contribute data
21 to RADARS. But one of the things in Dr. Perrin's slides
22 that she discussed, and I think this is going to be a

1 semantic issue, are that for most of the day, we've been
2 talking about abuse and misuse, and she spent a lot of
3 time talking about adverse events and poisoning and
4 overdose. The problem with that is that when we think
5 about overdose, we usually think about suicidality or
6 some other intent, which I guess my question really is:
7 How do we reconcile that as you try to figure out the
8 data? How do you integrate the terminology?

9 DR. COPLAN: So, as Dr. Perrin showed in her
10 slide, the adverse events really refer to overdoses and
11 poisonings associated with prescription opioids.
12 Specific ICD-9 codes 965.0 and EA-50, which is very
13 specific for poisoning and overdose. So, yes, when we
14 refer to adverse events, we're really referring to those
15 specific ICD-9 codes.

16 DR. NELSON: Right, but I guess my question is
17 when you look up an ICD-9 code for an overdose, you
18 might not be looking at an abuse or a misuse. You might
19 be looking at a suicidal patient, and when you look up
20 poisoning, it's a very vague term. Adverse event
21 usually generally means therapeutic misadventure, a
22 therapeutic problem.

1 DR. COPLAN: Yes, yes.

2 DR. NELSON: It could also mean a medical
3 error. I mean, these are terms that don't match very
4 well. And I guess since we're really talking about
5 misuse and abuse as a construct, I'm not sure how these
6 terms are going to easily equate to the terms that we're
7 interested in hearing about.

8 DR. COPLAN: Well, we categorized our outcomes
9 into measures of abuse, measures of routes of
10 administration, and changes in the overdose rates and
11 poisoning rates over time in essentially a cohort study
12 of the Kaiser membership population. So, what we're
13 looking at is changes over time. So, if there is some
14 misclassification, that should be consistent over time,
15 and, therefore, the trends in OxyContin versus a trend
16 in comparator opioids should be reasonably meaningful.

17 I agree with you that if that was as
18 foolproof, as bulletproof as a randomized, clinical
19 trial, where you specifically look for these endpoints
20 then we wouldn't have to do eight studies, we would just
21 do that one study.

22 DR. NELSON: Yes, I don't want to belabor it,

1 but I guess my question is: Why don't you look at
2 misuse and abuse as concepts within the KP data instead
3 of looking at these codes because they're not really
4 reconcilable? At least I don't think they're easily
5 reconcilable.

6 My other question--

7 DR. COPLAN: That is something we will
8 consider.

9 DR. NELSON: Yes. My other issue is, and I
10 want to second the comments about medical examiner data,
11 about death data because, I mean, clearly, one of the
12 big issues that we see with abuse and misuse as a very
13 defined endpoint is death. I've commented in the past,
14 and I'll comment at another time about the use of
15 medical examiner data to define abuse and misuse because
16 there are a lot of issues with that.

17 One of my concerns is that the two systems
18 you're going to use to look at death, one of them
19 involves the KP data. The other one involves the poison
20 center data, and as Rick Dart will elaborate on, if
21 you'd like, most deaths are not called into poison
22 centers. Right?

1 I mean, when we compared our data to medical
2 examiner data, we have only a fraction of the poisoning-
3 related deaths. And since many, if not most opioid
4 overdose-related deaths occur outside of a hospital,
5 we're going to miss the vast majority of overdoses. So,
6 without looking at some other database, meaning the
7 medical examiner database or some vital statistics
8 database, I think we're going to miss a lot of deaths.
9 Just looking at the two that you have, as some people
10 have already pointed out, is going to be very limiting.

11 DR. COPLAN: I fully agree with you. That's
12 one of the reasons why we use this case fatality rate
13 top of metric in the Poison Control Center, which hasn't
14 been used for an analytic type of study before,
15 precisely to address this concern because the case
16 fatality rate looks at the number of deaths per
17 exposures, and looking at whether it's changed in the
18 time of fatalities per exposures as one way of getting
19 at that. I don't think it's a perfect way.

20 DR. NELSON: Yes, my strong recommendation
21 would be to look at medical examiner data. With all its
22 limitations, it still will account for the majority of

1 the deaths, which I think you'll miss in this system.

2 DR. COPLAN: Yes. Nab, do you want to address
3 this? We're calling on someone from the other bullpen.

4 (Laughter.)

5 MR. DASGUPTA: My name is Nabarun Dasgupta. I
6 am with the University of North Carolina and Chapel
7 Hill, and I have no financial interest in this meeting,
8 but my way here has been paid for King.

9 The reason I'm up here is that we've been in
10 talks with Paul and the other folks at Purdue to do
11 exactly the study that you proposed, Dr. Nelson, and
12 what Dr. Paulozzi has proposed before, where we can link
13 the Prescription Monitoring Program to the medical
14 examiner data. We passed legislation in our state
15 earlier this year to allow for that linkage to happen.
16 The State Health Department has done a pilot study doing
17 the linkages between the Prescription Monitoring Program
18 and the medical examiner data in three counties. We
19 have a methodology for it, and we have agreement within
20 that state health government structure to go forward
21 with it.

22 That study is not presented here because it's

1 not formalized and hasn't been advanced enough at this
2 point to warrant full scientific scrutiny, but it is
3 something that we are looking at and have some
4 experience with, and are confident that we can do.

5 DR. COPLAN: So, essentially, what we're
6 planning to do is a repetition of the study Aaron Hall
7 and colleagues from the CDC that looked at linking state
8 medical coroner's reports for deaths in West Virginia in
9 the year of 2006 with Prescription Monitoring Programs
10 and state toxicology reports, and we would look at that
11 by looking at changes over time.

12 As Nab pointed out, we haven't presented that
13 yet today. We did actually mention it when first
14 submitted something to the FDA that that was a study
15 that we would like to do, but because of the feasibility
16 of integrating multiple state agencies and third-party
17 groups to do the statistical analysis, it would take
18 some time, particularly when working as a for-profit
19 company, a drug sponsor trying to get this study to
20 happen, it would take some careful negotiations to bring
21 together various state parties. But that is something
22 that we are actively pursuing, and we do seem to have an

1 avenue that's opening for that.

2 DR. KIRSCH: Before I call on the next person,
3 I want to remind the members of the committee we're
4 calling on people in order from when they raised their
5 hand. So, if you think we're ignoring you, we're not.
6 We'll get to you.

7 For the FDA, I actually have a question. With
8 a number of people who we have on the list to ask
9 questions, I think it's very likely we'll run over our
10 4:00 time, which, for me, as long as I get done by 9:00
11 to watch Oregon beat UCLA, I'll be okay.

12 (Laughter.)

13 DR. KIRSCH: But if we run a little bit over,
14 will that be a problem?

15 DR. RAPPAPORT: Well, I have a show on earlier
16 than that.

17 (Laughter.)

18 DR. RAPPAPORT: But I think it's your
19 discretion when to end the meeting.

20 DR. KIRSCH: Okay.

21 Ms. Krivacic?

22 MS. KRIVACIC: Thank you. I have a couple of

1 short questions. One is for Chilcoat. The question is
2 there was reference made to the materials that we
3 receive about the PRIDE Survey, the acronym PRIDE, and
4 if that is part of the surveys that will be utilized
5 here.

6 DR. COPLAN: Dr. Chilcoat?

7 DR. CHILCOAT: No, it's not. It actually only
8 grants one question about OxyContin. So, I think a lot
9 of the prevalence for that study is much higher than
10 what you see in other surveys, and, so, we decided not
11 to use it, even though we originally considered it.

12 MS. KRIVACIC: Thank you. My second question
13 refers back to slide 56, the case fatality rate, and I
14 was wondering if Dr. Dart can speak to teasing that data
15 out by way of age range, adolescence. Is that something
16 that you have access to? And then, also, can you tease
17 it out by even socioeconomic status?

18 Thank you.

19 DR. DART: That's a yes and a no. So, for
20 age, we can bring it out really of any single year you
21 want, any age range grouping you want, that can be done.
22 So, if we want to look at adolescence for new initiates

1 or into your 20s, we can do that. But when it comes to
2 socioeconomic status, we don't gather that information.
3 The reason is that this is an acute health care event.
4 So, the real reason of a poison center, of course, is to
5 give some advice to the caller or to the health care
6 provider who's calling, and, so, we don't ask a lot of
7 demographic questions since we're basically taking care
8 of the patient. So, yes.

9 DR. KIRSCH: Dr. Zeltermann?

10 DR. COPLAN: I'm sorry, could we have backup
11 55? Just to add to that response, if you wouldn't mind.

12 This is data broken down by, as Professor Dart
13 mentioned, this was somewhat arbitrary. We broke it
14 down into less than 12 and greater than 12 to see if we
15 could detect an effect specifically in the pediatric
16 population with the assumption that if a new formulation
17 didn't allow the extended-release mechanism to be so
18 easily broken by a kid, an infant or a child, they would
19 have more time to get into emergency department and get
20 a shot of naloxone and be able to save the kid. But,
21 unfortunately, there are only three deaths of--not
22 unfortunately. Sorry.

1 (Laughter.)

2 DR. COPLAN: For the purpose of this study,
3 there are rather few deaths to be able to make any
4 determination of that.

5 DR. KIRSCH: Dr. Zelterman?

6 DR. ZELTERMAN: A comment about the Internet
7 study and then the Kaiser Permanente Study.

8 My mother told me not to believe what I read,
9 and that's especially true of the Internet.

10 (Laughter.)

11 DR. ZELTERMAN: If you really want it, I mean,
12 by Monday morning, we could have 100,000 posts of what
13 you can do with OxyContin that defy your imagination.
14 What you can get out of the Internet is if somebody
15 really finds a way using common household methods of
16 extracting the slow release, and that's what you can
17 get. That's, I think, the only thing the Internet is
18 going to teach you that is if somebody figures that out.

19 As for the Kaiser Permanente, could I see
20 slide 42? Slide 42, these are the comparisons that are
21 going to be made, and Dr. Kirsch already pointed out
22 that the Kaiser Permanente data is not a random sample

1 from the population; it's a very biased sample. It's
2 subscribers of this health insurance. It's not clear
3 whether over a period of time the patients are changing,
4 the coverage is changing. It's not clear.

5 And then if I can go to slide 45, while you
6 address that. On slide 45, Dr. Perrin commented that
7 there are many different regions and different groups
8 that could be included, and if you want to get the point
9 0.05 significance in front of the FDA, I think you
10 usually have to specify your population before rather
11 than hunt around and find the ones that support your
12 hypothesis.

13 DR. PERRIN: Okay, so, we'll start with the
14 first issue. So, which slide were we on?

15 DR. COPLAN: Slide 42.

16 DR. PERRIN: Forty-two.

17 DR. COPLAN: Can you go back to 42?

18 DR. PERRIN: So, yes, there are changes in
19 membership over time, and there are also changes in
20 prescribing patterns over time. And that's why we feel
21 that using a time series design with a comparator is so
22 important. And, also, looking at this in different

1 subgroups where we know that there have been some
2 changes.

3 We can also add into our time series, and I
4 didn't go into this in detail, but we can add time
5 varying covariates into the model that will adjust for
6 these different trends over time, if necessary.

7 And, so, for the second one, I promise you I
8 won't hunt around for which regions are the right
9 regions, but what we do plan to do is, based on the size
10 of the region, figure out how many more regions we need
11 to bring in. So, we are not looking at data from any of
12 the other regions, we're only looking at the size of the
13 membership, and then we would begin to figure out which
14 ones to collaborate with and share our codes. So, we're
15 extracting records in exactly the same way.

16 DR. KIRSCH: Dr. Morrato?

17 DR. MORRATO: Yes, my question relates to your
18 interest in demonstrating sustainability and how you're
19 defining sustainability and duration of observation.
20 So, I understand and appreciate the rationale for the
21 time series, but it wasn't clear to me always what was
22 the unit of time that's being done in some of the

1 studies and how that might differ. And, therefore, how
2 many points you're actually looking at when you're
3 assessing trends. So, for instance, in the Kaiser
4 study, it looked like there's annual rates based on what
5 I saw, so, that would give you two time points. The
6 NSDUH survey, again, I think is annual. That gives you
7 two time points, and it's a two-year lag for the data.
8 So, it's actually four years out for that. and, so,
9 that's one question.

10 And related to that is, on the other hand, you
11 have some opportunity to get very discreet data, let's
12 say the Internet discussions or the abuser cohort in
13 Kentucky, and you only carry those studies out for six
14 to nine months. One might anticipate that that's going
15 to be an evolving market in which what you learn and
16 adapt to in the first few months is going to be very
17 different than how people might adapt a year later. So,
18 I don't know how that's supporting sustainability.

19 DR. COPLAN: Yes, that's something we've
20 discussed a lot. It's obviously a key issue.

21 Could I have back up slide 35?

22 So, this is the Kaiser data. So, one of the

1 questions was: What are the units? Is this annual?
2 This is actually in a six-month period. So, in two
3 years, we would have four periods. Some of the quotes
4 we've been seeing on the Internet, there's a real
5 aversion to the new formulation. We have seen methods
6 of tampering being posted by abusers on the Web Site,
7 but, as Dr. Zeltermann referred to, they are not
8 widespread.

9 So, definitely, we're going to see very
10 determined abusers finding ways to get around the
11 formulation. The question is whether 50 or 60 other
12 abusers say wow, this works for me, this is great, we
13 found a way, and we haven't see that. Other people say
14 well, I tried it and I spent two hours heating and
15 freezing and I didn't really get much of a high.

16 So, based on that, we would expect to see a
17 relatively quick change. And then the sustainability
18 then becomes what do we see over the four halves of the
19 year? As we mentioned, if it's a very clear trend, then
20 that would be evidence of sustainability. That does
21 mean, as we mentioned, that we would no longer monitor.
22 We have been monitoring adverse event rates for

1 OxyContin since 2002, created a system to do that since
2 the database didn't exist to do that, and we're
3 continuing to evolve new systems of surveillance that
4 use more complex geographic information systems to do
5 that, which we haven't discussed today.

6 We also have some collaborating evidence.
7 Could I have slide 573?

8 We have some collaborating evidence of changes
9 in prescribing. That suggest we would see a relatively
10 quick effect.

11 This is some data looking at change in
12 prescriptions of the new formulation and generic ER
13 oxycodone in the past eight weeks in health care
14 providers with questionable prescribing or medical
15 practices. Purdue keeps a database of prescribers who
16 through various sources of information, primarily the
17 field sales force, who has a very good handle on which
18 prescribers are problematic. So, we keep a list of
19 those prescribers to make sure that we do not call on
20 them. The field sales force does not them.

21 We've been tracking using the SDI data that
22 has been referred to earlier to look at changes in

1 prescriptions amongst these health care providers, and
2 we have some very preliminary data. I think it needs to
3 be further worked out, but for OxyContin, in the current
4 4 weeks, there were 10,700 prescriptions compared to the
5 previous 4 weeks of 16,000 prescriptions for a reduction
6 of 5,000 prescription or minus 34 percent.

7 For ER generic oxycodone, they were smaller in
8 absolute numbers, but there was a increase in
9 prescriptions in the 8-week period for a net increase of
10 24 percent. And for the total ER oxycodone brand and
11 generic, we've seen a reduction of 27 percent. Now
12 this, obviously, has many flaws in it.

13 We need to compare these with 1,300
14 prescribers on the do-not-call list, we need to look at
15 comparing prescribers who are not on the do-not-call
16 list, but this suggests that we're likely to see a
17 relatively quick effect, and that four subsequent
18 measures would be reasonable. If it's not, we are
19 perfectly willing to continue to survey this as long as
20 it's needed.

21 DR. KIRSCH: Dr. Omoigui?

22 DR. OMOIGUI: I am wondering, bring back the

1 slide 35 again. And ask if the others can do two
2 opioids. Were those short-acting, long-acting, or both?

3 DR. COPLAN: That's a mixture. The hierarchy
4 in determining this was first OxyContin or ER oxycodone,
5 then other oxycodone, which would be the immediate-
6 release oxycodone single and combination, and then other
7 Schedule IIs would be hydrocodone, methadone, fentanyl
8 patch.

9 PARTICIPANT: Not hydrocodone.

10 DR. COPLAN: Sorry, not hydrocodone. Thank
11 you. Hydrocodone would be Schedule III. So, yes.

12 DR. OMOIGUI: Okay, if we look again at this
13 slide 53 and 83, it looks like in the last few years
14 there's an increasing trend in the greater abuse and
15 diversion of the immediate-release oxycodone as compared
16 to the OxyContin, and I believe during those few years
17 was when we've had increased dose trends of some of the
18 immediate-release oxycodone. I think the 30 mgs came
19 out in the last few years.

20 So, the question is this then: Are we already
21 seeing a trend away from OxyContin into the immediate-
22 release oxycodone, and if we are doing that, are we

1 going to be proactive in the fact that if this new
2 reformulated OxyContin is successful, you're going to
3 see a shift, an even greater shift into the immediate-
4 release because the drug abuse problem is not going to
5 go away quietly into the night.

6 It's going to try and shift, and we have to be
7 proactive in checking that out. And I noticed that some
8 of your studies, you are assessing the impact of the new
9 formulation on the abuse of the immediate-release.

10 Is there a way you can do that in all your
11 studies so that that way if you're seeing a reduction in
12 the abuse of the OxyContin you can tie it into any
13 changes in abuse of the immediate-release formulations?

14 DR. COPLAN: Good, thank you for that
15 question. So, we'll look at it in two ways. First, we
16 will look at the data to estimate is there a shift
17 occurring, and, secondly, Dr. Landau will address the
18 issue of a potential shifting.

19 Nelson, could I have backup slide 30? Thank
20 you.

21 So, as mentioned earlier, even before the new
22 formulation of OxyContin came out. This is data going

1 up to 2009, and this is data that was presented by the
2 FDA at the last adcom that this group had. If you look
3 at the single ingredient oxycodone, it has increased 660
4 percent, whereas extended-release oxycodone has
5 increased by 40 percent in the last 10 years. So, we
6 have been seeing a dramatic shift already occurring
7 independent of any new formulation of extended-release
8 oxycodone.

9 There was also a discussion at the last
10 advisory committee around what was the predominant drug
11 that was being dispensed in the Florida pill mills
12 which, as we all know, is one of the worst sources of
13 opioids for the purposes of abuse. And some people said
14 well, it was OxyContin that was the most prescribed in
15 the Florida pill mills. And then someone who's on the
16 board of directors of the Florida pill mills said no,
17 it's shifted. It's now immediate-release single
18 ingredients oxycodone, and we don't actually have data
19 on that.

20 We're trying to look to see if we can actually
21 get data on that, but, based on that discussion, there
22 has been some evidence of the Florida pill mills

1 reducing their prescription. Not that they stopped
2 prescribing OxyContin, but there's a reduction in the
3 overall patent, and that's largely because the DEA was
4 using certain prescribing metrics to determine who to
5 arrest.

6 And so, if you look back in Google, you can
7 get the information of which providers were arrested by
8 DEA. Initially, they were arrested because the major
9 flag was that they were prescribing most 60 and 80 mg
10 OxyContin and for cash payments. So, once a couple of
11 people got arrested for that, then people adapted.

12 So, we're already seeing a shift occurring,
13 and now we'll talk about the second part of the problem
14 is how we do address the public health impact of this
15 formulation potentially adding to that shift?

16 DR. LANDAU: Thank you Paul. I would only add
17 that it's an unfortunate reality, but it is our
18 expectation that if we're successful with the
19 formulation, that abusers will shift either to other
20 routes of abuse that are more practical to them or to
21 other drugs. We've seen evidence that this is occurring
22 already in close to real time through Internet

1 monitoring. We expect to see a significant reduction in
2 intravenous abuse and intranasal abuse. I think it
3 speaks to the complexity and the limited role one
4 pharmaceutical company can play in a multi-factorial
5 problem. And I think it's an excellent question.

6 Thank you.

7 DR. COPLAN: If I could add one thing, as we
8 mentioned--

9 DR. KIRSCH: Well, if it's critical. We are
10 out of time.

11 DR. COPLAN: Sorry.

12 DR. KIRSCH: So, I'm going to go through a
13 couple more of these.

14 Dr. Bickel?

15 DR. BICKEL: First, I want to commend the FDA
16 and the Sponsor for presenting very interesting and
17 important sets of presentations today.

18 For the Sponsor, and I guess Dr. Landau, I'd
19 like to understand what the company's response would be
20 under two sets of circumstances. One, the set of eight
21 studies produced results that are inconsistent, or,
22 alternatively, the set of eight studies suggests that

1 the problem is actually getting worse or staying the
2 same?

3 DR. LANDAU: Well, in either scenario, we'd be
4 interpreting and discussing the results of the studies,
5 as Dr. Coplan mentioned, on a periodic basis, reviewing
6 them internally with our expert panel, and sharing the
7 results with the Agency. It's hard to predict how we
8 would respond, given the complex nature of the problem
9 and the complex interrelationship with some of the
10 behaviors and the outcomes these studies are intended to
11 measure.

12 What I can tell you is that we're very
13 interested in measuring and monitoring, and we have been
14 and will continue to be very proactive in our actions,
15 and they're be appropriate and shared with the
16 regulators.

17 Thank you.

18 DR. COPLAN: We think that the cornerstone of
19 determining whether these studies are demonstrating an
20 effect will ultimately be expert judgment that will
21 involve clinical, statistical, and epidemiological
22 expertise.

1 DR. KIRSCH: Dr. Morris-Kukoski?

2 DR. MORRIS-KUKOSKI: I have two questions.

3 One is since you said you're already collecting data as
4 of August, but you realize that the market is still
5 going to continue to have the old formulation of the
6 OxyContin through the first of the year. Are you not
7 going to then shift your data that you're actually
8 looking at so you actually have this slight overlap so
9 you can continue past that period of time when we know
10 the regular OxyContin or the old formula is still out
11 there? That's my first question.

12 DR. COPLAN: We thought a lot about how to do
13 that because that is a key issue. For trends, for
14 determining a pre-post change between two incidence
15 rates, we would need to take that mixed time out,
16 perhaps that one quarter. For trends, that reduction
17 over time becomes important for us to include.

18 DR. MORRIS-KUKOSKI: And my second question
19 is: Is your definition for more difficult to manipulate
20 only crushing with spoons and dissolving with water?

21 DR. LANDAU: I'm going to call up a slide in a
22 moment. The short answer to the question is no. In

1 March of 2009, we submitted along with our resubmission
2 to a complete response letter to the division the
3 results from seven separate and comprehensive in vitro
4 studies, and I mentioned earlier very briefly they were
5 designed with the assistance of experts and abuse in
6 tablet tampering and extraction techniques and even drug
7 enforcement. The results tell us a great number of
8 things, and the interpretation goes well beyond more
9 difficult to crush and inject.

10 May I have slide--

11 DR. KIRSCH: Is the slide different than what
12 you've just said?

13 DR. LANDAU: Slide 481, please. Yes.

14 Okay, so, shown here, the experiments
15 replicated proceed replicated techniques of tablet
16 tampering that are relevant both to the abuse and the
17 patient error context, and I don't have a pointer here,
18 but under "Route," what's common to each one of these
19 circumstances or settings is, in many cases, all, with
20 the exception, frankly, of swallowing intact tablets, is
21 some degree of physical or chemical manipulation. So,
22 the seven separate experiments were designed, as

1 represented here, to inform a prediction for how
2 difficult or what incremental change would exist for
3 this formulation relative to the original formulation in
4 both the patient and the abuser setting.

5 On the right margin, you see are sort of the
6 results broadly characterized for a public setting like
7 this, and in each scenario of testing or each access of
8 testing, the new formulation, the reformulation was,
9 well, in most all, more robust or more difficult to
10 manipulate or convert to a dose form that was necessary
11 to abuse via one or more of these routes and never
12 worse.

13 DR. KIRSCH: Thank you.

14 Dr. Mendelson?

15 DR. MENDELSON: Yes, hi. Just a couple of
16 quick points.

17 First, the one thing that does seem to be
18 missing is the economic data again, and I think you
19 could collect this through Kaiser. How much do people
20 pay as a co-payment for their prescriptions? I think
21 that would be very useful information. If it costs
22 twice and much to get one and people prefer that, that's

1 actual news, that it's the Dr. Bickel's behavioral
2 economics.

3 Second, I think it's ironic that the FDA
4 requires suicide assessments for almost all new drug
5 evaluations right now, yet, suicide is not explicitly
6 parsed out or separated in this analysis. I think you
7 guys have an inconsistency with your other drug programs
8 by not making suicide explicitly separated in the
9 overdose data. And if a lot of these overdose deaths
10 are suicides either intentional with drug intoxication
11 or during withdrawal because they can't obtain the drug,
12 that would be big news.

13 And finally, I would note that Purdue does
14 make immediate-release oxycodone. It sells two brands
15 of that. We just looked it up on Epocrates here. And,
16 so, you guys might be back here with more trouble in the
17 future. You may want to address that now and actually
18 ask what's going on with your IR oxycodone products as
19 they move up the ladder of acceptability and
20 preferability in addicts.

21 DR. LANDAU: Sure. I'd like to address I
22 guess the latter part of your series of questions, the

1 last one. We no longer manufacturer and market
2 immediate release oxycodone, just for a point of
3 clarity.

4 DR. KIRSCH: Thank you.

5 Could you pull up slide 119, please?

6 DR. COPLAN: We had some data on prospect.

7 DR. KIRSCH: The question that I have about
8 119 is it was unclear to me how the data is going to be
9 delivered to the FDA. Will it be delivered from these
10 individual studies after being filtered through the
11 company or will they investigate individual groups doing
12 the investigation, report directly to the FDA?

13 DR. COPLAN: The nature of FDA's reporting
14 mechanism is that the sponsors were responsible for
15 providing an annual report on whatever timeframe the FDA
16 deems is appropriate. Generally, it's annually.

17 What we have stated here is that we would
18 include a PDF that's obtained from the investigators of
19 the study, Dr. Perrin, Dr. Dart, Dr. Cassidy, and submit
20 those as part of the report with an overall integration
21 by the expert panel and by Purdue. It's two separate.

22 DR. KIRSCH: That is--

1 DR. RAPPAPORT: Jeff?

2 DR. KIRSCH: Yes.

3 DR. RAPPAPORT: Can I clarify something about
4 that? I mean, everything that comes into the agency
5 comes in through the sponsors. Occasionally, we do get
6 citizen's petitions and things like that, but in regard
7 to an application, it comes from a sponsor. But we have
8 a long history of investigating data integrity, and we
9 get all of the data and the raw data, as well. So, we
10 look at that very carefully to make sure that what
11 they've synopsisized for us is consistent with the raw
12 data and we go out and investigate their sites and all
13 of that.

14 DR. KIRSCH: Thank you.

15 Dr. Denisco?

16 MR. DENISCO: Asked and answered.

17 DR. KIRSCH: Asked and answered.

18 Dr. Flick?

19 DR. FLICK: That was my question.

20 DR. KIRSCH: Dr. Kerns? Last question.

21 DR. KERNS: I'll wait until tomorrow.

22 DR. KIRSCH: Okay. With that, we'll adjourn

1 the meeting. Thanks, everybody for their attention.

2 DR. COPLAN: Thank you.

3 (Whereupon, at 4:07 p.m., the meeting was
4 adjourned.)

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21